이학석사학위논문

일련 작용 전략을 이용한 새로운 금 촉매 반응의 개발

The Development of New Gold-Catalyzed Reactions Using a Tandem Strategy

2016년 2월

서울대학교 대학원
화학전공
김 상 민

일련 작용 전략을 이용한 새로운 금 촉매 반응의 개발

The Development of New Gold-Catalyzed Reactions Using a Tandem Strategy

지도교수 Soon Hyeok Hong
이 논문을 이학석사학위논문으로 제출함

2015년 12월

서울대학교 대학원
화 학 부
김 상 민

김상민의 석사학위논문을 인준함
2015년 12월

위 원 장 정 영 근 (인)
부 위 원 장 Soon Hyeok Hong(인)
위 원 이 철 범 (인)

Abstract

The Development of New Gold-Catalyzed Reactions Using a Tandem Strategy

Sangmin Kim
The Department of Chemistry
The Graduate School
Seoul National University

Recently, tandem reactions have been issued in organic synthesis area due to its step-economical advantage. A novel strategy for enamide synthesis from primary amides and propargyl aldehydes via Au(I)-catalyzed tandem amide addition and Meyer-Schuster rearrangement is described. In situ generated hemiaminals were successfully converted to the desired products under the optimized conditions. Enamide stereochemistry was controlled simply by changing solvents and adding a catalytic amount of acid. The developed synthetic strategy provides a new method to synthesize various β-substituted-α,β-unsaturated carbonyl compounds.

keywords : Gold-Catalysis, Tandem, Enamide, Stereochemistry

***Student Number* : 2014 - 20308**

Table of Contents

List of Schemes

List of Tables

Gold(I)-Catalyzed, Stereocontrolled Enamide Synthesis from Primary Amides and Propargyl Aldehydes Using a Tandem Strategy†

Abstract

A novel strategy for enamide synthesis from primary amides and propargyl aldehydes via Au(I)-catalyzed tandem amide addition and Meyer-Schuster rearrangement is described. In situ generated hemiaminals were successfully converted to the desired products under the optimized conditions. Enamide stereochemistry was controlled simply by changing solvents and adding a catalytic amount of acid. The developed synthetic strategy provides a new method to synthesize various β-substituted-α,β-unsaturated carbonyl compounds.

Introduction

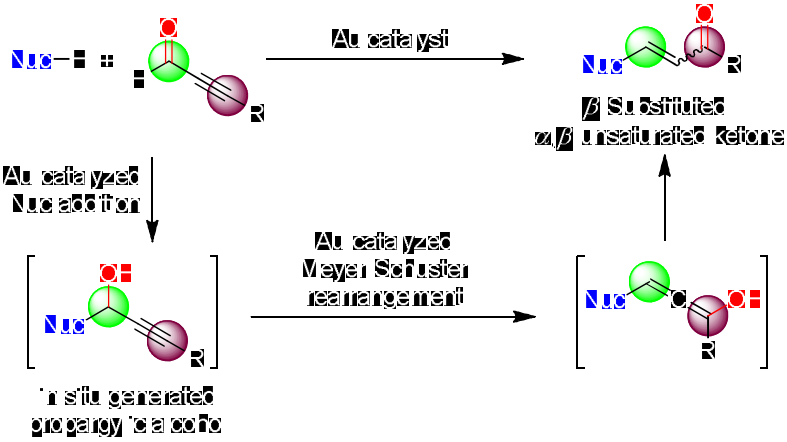
Enamides are very common organic compounds and encompass numerous natural products and drug candidates.[1] In addition, enamides are highly valuable synthetic intermediates for the synthesis of chiral amines,[2] heterocycles,[3] and cross-coupling reagents.[4] Several synthetic methods for the preparation of enamides have already been developed, such as the dehydration of hemiaminals,[5] condensation of compounds containing carbonyl functional groups with amides,[6] and acylation of imines;[7] however, these conventional methods require harsh reaction conditions and provide poor stereoselective control. Recently, diverse transition metal-catalyzed reactions have been developed utilizing Ru,[8,9] Rh,[8] Fe,[8] Pd,[10] Au,[11] and Cu,[12] which provide significant advantages over traditional methods. Nevertheless, these reactions are also limited due

† The majority of this work has been published: Kim, S. M.; Lee, D.; Hong, S. H. *Org. Lett.* **2014**, *16*, 6168-6171.

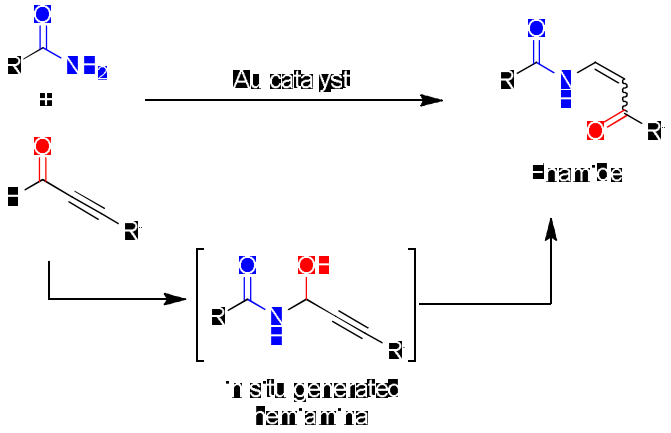
to difficulties in preparing the necessary starting materials, requirement of particular reaction conditions, and confined scope of the enamide products. Therefore, new, simple synthetic strategies are still needed.

The Meyer-Schuster rearrangement of propargylic alcohols is a powerful tool to make α,β-unsaturated ketones,[13] allowing for the synthesis of many β-functionalized compounds from diverse substrates. Within the last decade, many Au(I)- and Au(III)-catalyzed Meyer-Schuster rearrangement reactions have been developed.[14] However, the propargylic alcohols are mostly confined to alkyl or aryl substitution at the propargylic position. Applying this reaction to the more inherently unstable substrates with a carbon-heteroatom bond at the propargylic position, such as propargylic hemiaminal, would significantly extend the synthetic possibilities. To overcome the limitation, we envisioned the use of in situ generation of heteroatom-substituted propargylic alcohols from readily available nucleophiles and propargyl aldehydes (Scheme 1). In this regard, the rearrangement of propargylic hemiaminals synthesized from primary amides and propargyl aldehydes would yield particularly valuable enamides. Au catalysis appeared to be most promising to achieve this goal, given that it can activate propargyl aldehydes to yield more electrophilic species[15] and also can mediate the Meyer-Schuster rearrangement of propargylic alcohols.

a. Tandem Strategy : Nucleophilic addition and Meyer-Schuster rearrangement



b. Enamide synthesis from primary amides and propargyl aldehydes



Scheme 1. Novel Synthetic Strategy for β-Substituted-α,β-Unsaturated Ketones via Tandem Nucleophilic Addition and Meyer-Schuster Rearrangement

Results & Discussion

A model reaction between benzamide (**1a**) and 2-octynal (**2a**) was first used to determine the required catalytic conditions (Table 1), beginning by determining the ideal Au catalyst. The simpler Au(I) and Au(III) chloride catalysts showed low activity (entries 1 and 2), while the addition of AgOTf increased the yield slightly to 40% (entry 3). While the N-heterocyclic carbene (NHC)-based Au catalyst (IPr)AuCl did not result in a meaningful improvement in yield (entry 4), Ph_3PAuCl showed significantly greater activity, producing the enamide in 56% yield (entry5). This result suggested that phosphine-based Au complexes might provide the best results; testing of several of these catalysts identified Me_4*t*BuXPhosAuCl (**L**AuCl) as the best candidate (entries 6 and 7). Further testing of the Ag additive confirmed triflate and tosylate to be the best counterions (entries 7 - 10). Meanwhile, solvent testing revealed that THF gave the highest yields (entries 7, 11, and 12). Interestingly, decreasing solvent polarity increased the *Z*/*E* ratio of the product; while DCM yielded the highest ratio of 19 (entry 11), DMF gave the *E*-enamide as the major isomer (entry 12). Water and ethanol additives increased the yield to 89%, an observation that is consistent with previous results;[14] because AgOTf gave a slightly better yield than AgOTs under the optimized conditions, it was selected for further study (entries 13 and 14).

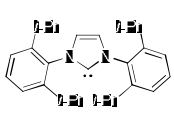
1a 2a 3aa : 4aa

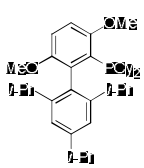
3aa, Z-enamide

4aa, E-enamide

entry	catalyst	additive	solvent	yield(%)[b]	Z/E[b]
1	$AuCl_3$	–	THF	19	5.6
2	AuCl	–	THF	29	5.4
3	AuCl/AgOTf	–	THF	40	4.8
4	(IPr)AuCl/ AgOTf	–	THF	44	4.8
5	Ph_3PAuCl/ AgOTf	–	THF	56	4.7
6	BrettPhosAuCl /AgOTf	–	THF	55	5.2
7	LAuCl/AgOTf	–	THF	69	4.9
8	LAuCl/AgOTs	–	THF	71	6.6
9	LAuCl/$AgBF_4$	–	THF	56	5.7
10	L$AuNTf_2$	–	THF	43	5.7
11	LAuCl/AgOTf	–	DCM	38	19
12	LAuCl/AgOTf	–	DMF	29	0.7
13[c]	LAuCl/AgOTf	1.0 equiv H_2O& 0.5 equiv EtOH	THF	89	4.9
14[c]	LAuCl/AgOTs	1.0 equiv H_2O& 0.5 equiv EtOH	THF	85	5.0

[a]Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2a** (0.25 mmol, 1.0 equiv), catalyst (5 mol %), solvent (0.5 mL), 24 h. [b]Yield of isomeric mixtures and Z/E ratio determined by ^{1}H NMR. Mesitylene was used as an internal standard. [c]**2a** (0.30 mmol, 1.2 equiv) was used.





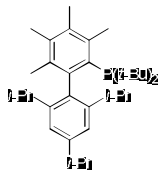
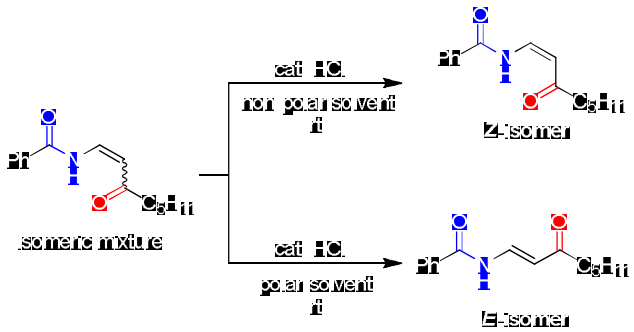


Table 1. Optimization of Reaction Conditions

Given the observed stereoselective solvent dependency in the screening experiments, additional solvents were tested to further improve the reaction utility (Table 2). A catalytic amount of HCl was added to facilitate isomerization through protonation of the carbonyl oxygen. As it has been previously reported, DCM predominantly gave the *Z*-isomer due to intramolecular hydrogen bonding between the amide proton and the carbonyl oxygen of the ketone group;[10e] unfortunately, less polar solvents could not be tested due to solubility issues. On the other hand, polar solvents, particularly DMSO, disrupted that intramolecular hydrogen bond by competing with the substrate, favoring the *E*-isomer as a result. Chang and co-workers reported that some *E*-enamides could be obtained by photoisomerization of the corresponding *Z*-enamides with moderate efficiency and selectivity by using 350 nm UV light.[10e] In our case, a simple work-up involving catalytic addition of HCl and careful solvent selection produce a similar, more selective result without any loss of the enamide product.

With the above results in hand, we investigated substrate scope with one-pot procedure including Au-catalyzed enamide synthesis and enamide isomerization to obtain *Z*-enamide selectively. First, amide substrate scope with **2a** was examined (Scheme 2). Several substituted benzamides afforded *Z*-enamides in reasonably high yields, including both those that contained electron-donating and electron-withdrawing groups (**3aa** - **3ia**). Hydroxy and halide substituents were both well tolerated by the reaction (**3ea**, **3ga-3ha**), while aliphatic amides gave good yields when two equivalents of aldehyde were used (**3ja** - **3la**). While cinnamamide and furanamide afforded moderate yields (**3ma-3na**), nicotinamide showed no reactivity (**3oa**).

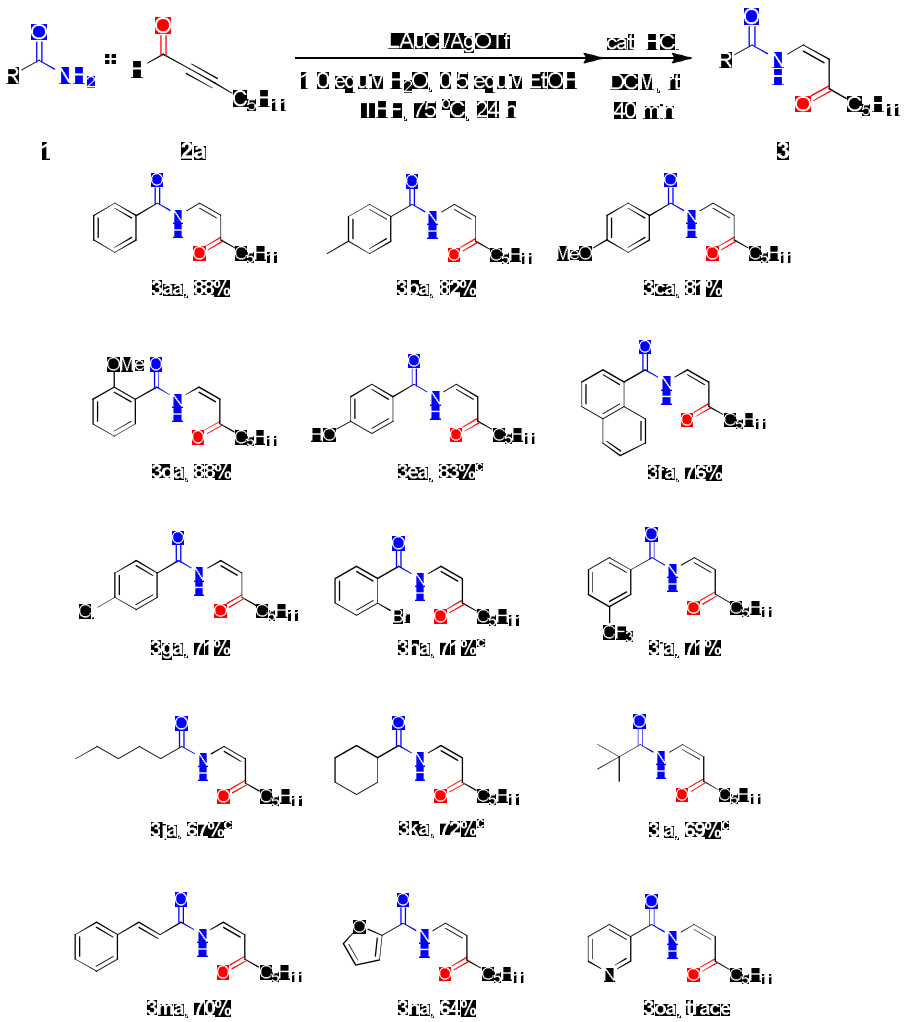


entry	solvent	Z:E^a
1	DCM	19 : 1
2	THF	5 : 1
3	MeOH	1.1 : 1
4	DMA	1 : 1.3
5	DMF	1 : 1.5
6	DMSO	1 : 8.6

[a] Z:E ratio was determined by ^{1}HNMR.

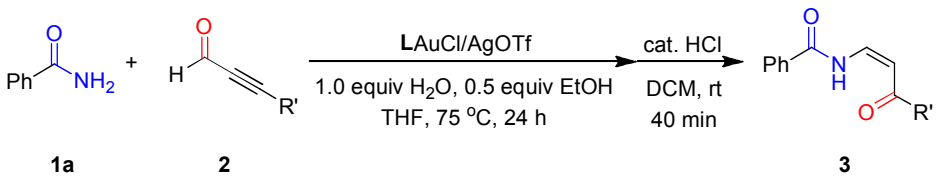
Table 2. Stereocontrolled Isomerization of Enamides

Next, aldehyde substrate scope was investigated with benzamide (Scheme 3). As opposed to the amides, aliphatic substitution gave higher yields than aryl substitution, even for sterically hindered substrates (**3aa**–**3ad**); aryl propargyl aldehydes only gave yields up to 73% (**3ae**–**3ai**). Notably, the aryl aldehyde 4-(3-oxo-1-propyn-1-yl)benzaldehyde (**2i**) only allowed for reaction at the propargyl aldehyde site (**3ai**).

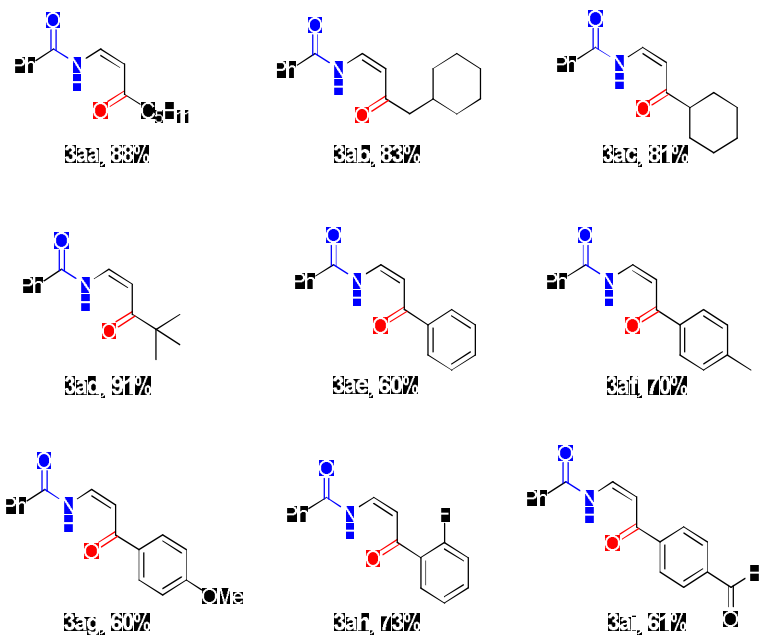


[a]Reaction conditions: step 1) **1** (0.25 mmol, 1.0 equiv), **2a** (0.30 mmol, 1.2 equiv), LAuCl (0.0125 mmol, 5 mol %), AgOTf (0.0125 mmol, 5 mol %), H_2O (0.25 mmol, 1.0 equiv), EtOH (0.125 mmol, 0.5 equiv), THF (0.5 mL), 75 °C,24 h; step 2) 4 M HCl in dioxane (0.0125 mmol, 5 mol %), DCM (0.5 mL), room temperature, 40 min. [b]Isolated yield. [c]**2a** (0.50 mmol, 2.0 equiv) was used.

Scheme 2. Amide Substrate Scope[a,b]



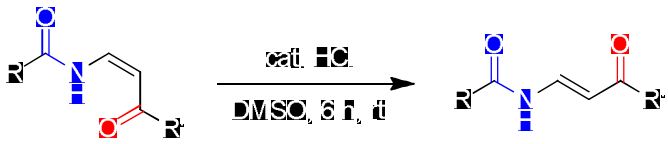
1a **2** **3**



[a]Reaction conditions: step 1) **1a** (0.25 mmol, 1.0 equiv), **2** (0.30 mmol, 1.2 equiv), **L**AuCl (0.0125 mmol, 5 mol %), AgOTf (0.0125 mmol, 5 mol %), H_2O (0.25 mmol, 1.0 equiv), EtOH (0.125 mmol, 0.5 equiv), THF (0.5 mL), 75 °C, 24 h; step 2) 4 M HCl in dioxane (0.0125 mmol, 5 mol %), DCM (0.5 mL), room temperature, 40 min. [b]Isolated yield.

Scheme 3. Aldehyde Substrate Scope

The developed isomerization method was then applied to obtain *E*-enamides from the various *Z*-enamides (Table 3). As expected, all chosen enamides showed good *E*-selectivity in DMSO. Generally, electron-deficient enamides gave higher *E*/*Z* ratios, presumably due to weaker intramolecular hydrogen bonding.

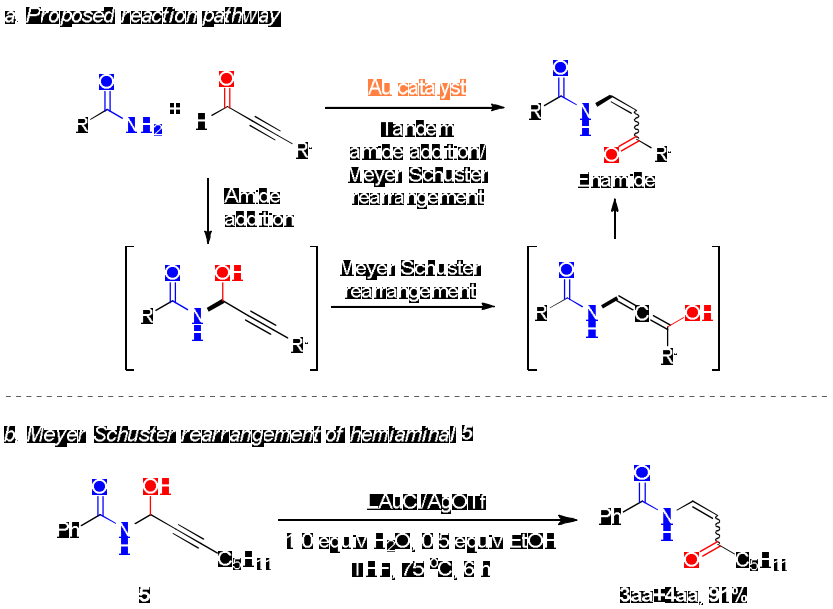


entry	R	R'	*E*/*Z*[b]
1	Ph	*p*-$MeOC_6H_4$	3.4
2	Ph	*t*-Bu	4.0
3	Ph	Ph	6.2
4	Ph	*n*-C_5H_{11}	8.6
5	Ph	*o*-FC_6H_4	9.9
6	*t*-Bu	*n*-C_5H_{11}	3.8
7	*p*-$MeOC_6H_4$	*n*-C_5H_{11}	7.0
8	*n*-C_5H_{11}	*n*-C_5H_{11}	11
9	*m*-$CF_3C_6H_4$	*n*-C_5H_{11}	17

[a]Reaction conditions: *Z*-enamide (1.0 equiv), 4 M HCl in dioxane (10 mol %), DMSO (0.5 mL), 6 h. [b]Determined by ^{1}H NMR.

Table 3. *E*-Selective Enamide Isomerization[a]

Finally, the reaction pathway was investigated to confirm that hemiaminals are produced as intermediates in this reaction (Scheme 4). An isolable hemiaminal (**5**) afforded the desired enamide product in 91% yield after 6 h under the optimized conditions, providing further support for the proposed mechanism.



Scheme 4. Proposed Reaction Pathway and Intermediate Study

Conclusion

In summary, a novel enamide synthesis has been developed that combines primary amides and propargyl aldehydes via Au(I)-catalyzed tandem amide addition and Meyer-Schuster rearrangement. Enamide stereoselectivity was controlled simply by changing solvents and through the addition of a catalytic amount of acid. The developed synthetic strategy provides a new approach by which to synthesize various β-substituted-α,β-unsaturated carbonyl compounds.

References

(1) Yet, L. *Chem. Rev.* **2003**, *103*, 4283.

(2) (a) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363. (c) Sibi, M. P.; Asano, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9708. (d) Blaser, H.-U.; Malan, C.;

Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.

(3) Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801.

(4) Roff, G. J.; Lloyd, R. C.; Turner, N. J. *J. Am. Chem. Soc.* **2004**, *126*, 4098.

(5) (a) Wang, X.; Porco, J. A. *J. Org. Chem.* **2001**, *66*, 8215. (b) Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665.

(6) (a) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479. (b) Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832.

(7) (a) Boeckman, R. K.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.

(8) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.

(9) (a) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413. (b) Gooβen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4042. (c) Gooβen, L. J.; Salih, K. S.; Blanchot, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 8492.

(10) (a) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (b) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845. (c) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. (d) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synthesis* **2005**, 3229. (e) Lee, J. M.; Ahn, D.-S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. *J. Am. Chem.*

Soc. **2006**, *128*, 12954. (f) Panda, N.; Mothkuri, R. *J. Org. Chem.* **2012**, *77*, 9407.

(11) Kimber, M. C. *Org. Lett.* **2010**, *12*, 1128.

(12) (a) Zhou, Y.-G.; Yang, P.-Y.; Han, X.-W. *J. Org. Chem.* **2005**, *70*, 1679. (b) Bolshan, Y.; Batey, R. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2109.

(13) (a) Meyer, K. H.; Schuster, K. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 819. (b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149. (c) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015.

(14) (a) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027. (b) Lee, S. I.; Baek, J. Y.; Sim, S. H.; Chung, Y. K. *Synthesis* **2007**, 2107. (c) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 0949. (d) Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem. - Eur. J.* **2007**, *13*, 6437. (e) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, 6988. (f) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *10*, 1867. (g) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767. (h) Ramón, R. n. S.; Gaillard, S.; Slawin, A. M. Z.; Porta, A.; D'Alfonso, A.; Zanoni, G.; Nolan, S. P. *Organometallics* **2010**, *29*, 3665. (i) Pennell, M. N.; Unthank, M. G.; Turner, P.; Sheppard, T. D. *J. Org. Chem.* **2011**, *76*, 1479. (j) Gómez-Suárez, A.; Oonishi, Y.; Meiries, S.; Nolan, S. P. *Organometallics* **2013**, *32*, 1106. (k) Hansmann, M. M.; Hashmi, A. S. K.; Lautens, M. *Org. Lett.* **2013**, *15*, 3226.

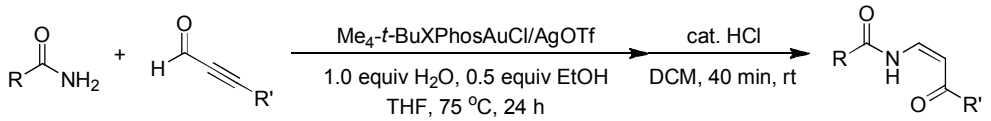
(15) Bhunia, S.; Abu Sohel, S. M.; Yang, C.-C.; Lush, S.-F.; Shen, F.-M.; Liu, R.-S. *J. Organomet. Chem.* **2009**, *694*, 566

Experimental Section

1. General information

Unless otherwise noted, all reactions were set up in a 4-mL vial under inert conditions. All anhydrous solvents were purchased from commercial suppliers and degassed with dry argon before usage. All amides, gold catalysts, silver salts, additives and two aldehydes (**2a** and **2e**) were purchased from commercial suppliers and used as received without further purification. Aldehydes (**2c**,[1] **2d**,[2] **2f**,[3] and **2g**[4]) were prepared following the literature procedures. NMR spectra were recorded in $CDCl_3$, THF-d_8, MeOD, DMA-d_9, DMF-d_7 and DMSO-d_6, and residue solvent signals were used as references. Ultra High Resolution ESI Q-TOF Mass spectrometer was performed by Organic Chemistry Research Center (OCRC) of Sogang University. HRMS-FAB was performed by the National Center for Inter-University Research Facilities of Seoul National University (NCIRF).

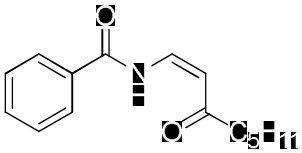
2. General procedure for Au(I)-catalyzed *Z*-enamide synthesis from primary amides and propargyl aldehydes



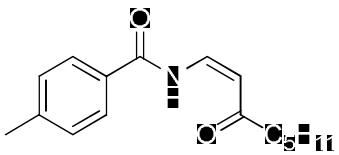
Me_4-*t*-BuXPhosAuCl (8.91 mg, 0.0125 mmol), AgOTf (3.21 mg, 0.0125 mmol), and THF (0.5 mL) were added to an oven dried 4 mL vial equipped with septum screw cap inside a glove box. Amide **1** (0.25 mmol) and aldehyde **2** (0.30 mmol or 0.50 mmol) were added also in the glove box. Then, outside the glove box, H_2O(4.5μL, 0.25 mmol) and EtOH (7.3 μL, 0.125 mmol) were added into the vial using micro-syringe. The vial was wrapped with aluminum foil. The

reaction mixture was stirred for 24 h at 75℃. After the reaction, all the volatiles of crude reaction mixture were removed under vacuum. DCM (0.5 mL) and 4 M HCl in dioxane (3.1 μL, 0.0125 mmol of HCl) were added to the crude residue in sequence under the air. The reaction mixture was stirred for 40 min at room temperature. After the reaction, all the volatiles were removed in vacuo. Purification of the crude products was performed with silica gel column chromatography using hexane and ethyl acetate solvent mixture as an eluent to afford the corresponding *Z*-enamide.

3. Characterization data

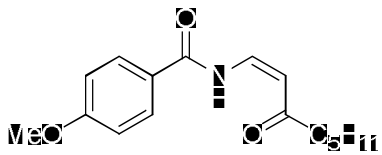


***N*-((*Z*)-3-oxooct-1-enyl)benzamide (3aa):** Pale yellow oil (53.8 mg, 0.219 mmol, 88%, Hex/EA = 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.56 (d, *J* = 9.2 Hz, 1 H), 7.99 (d, *J* = 7.5 Hz, 2 H), 7.79 – 7.39 (m, 4 H), 5.65 (d, *J* = 8.5 Hz, 1 H), 2.50 (t, *J* = 7.4 Hz, 2 H), 1.65 (quin, *J* = 7.3 Hz, 2 H), 1.33 (dd, *J* = 3.5, 7.3 Hz, 4 H), 0.90 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.8, 165.4, 138.1, 133.2, 132.2, 129.1, 128.1, 104.7, 43.7, 31.6, 24.4, 22.7, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{15}H_{19}NNaO_2$, 268.1308; found: 268.1305.

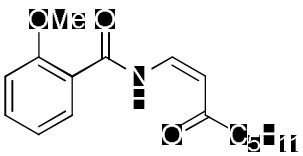


4-methyl-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ba): Yellow oil (53.4 mg, 0.206 mmol, 82%, Hex/EA = 12:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.50 (d, *J* = 10.2 Hz, 1 H), 7.87 (d, *J* = 8.3 Hz, 2 H),

7.64 (dd, J = 8.5, 10.7 Hz, 1 H), 7.27 (d, J = 8.1 Hz, 2 H), 5.62 (d, J = 8.5 Hz, 1 H), 2.48 (t, J = 7.4 Hz, 2 H), 2.40 (s, 3 H), 1.81 – 1.53 (m, 2 H), 1.47 – 1.21 (m, 4 H), 1.03 – 0.75 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.7, 165.3, 144.0, 138.3, 129.8, 129.4, 128.2, 104.4, 43.7, 31.6, 24.5, 22.7, 21.8, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{16}H_{21}NNaO_2$, 282.1465; found: 282.1466.

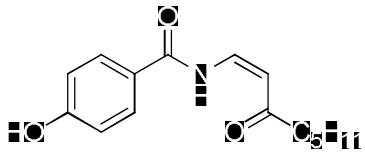


4-methoxy-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ca): Yellow solid (55.5 mg, 0.202 mmol, 81%, Hex/EA = 8:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.53 (d, 1 H), 8.10 – 7.90 (m, 2 H), 7.68 (dd, J = 8.5, 10.7 Hz, 1 H), 7.08 – 6.94 (m, 2 H), 5.65 (d, J = 8.5 Hz, 1 H), 3.90 (s, 3 H), 2.52 (t, J = 7.5 Hz, 2 H), 1.77 – 1.57 (m, 2 H), 1.43 – 1.30 (m, 4 H), 0.99 – 0.88 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.9, 165.0, 163.8, 138.7, 130.4, 124.6, 114.5, 104.2, 55.9, 43.8, 31.8, 24.6, 22.8, 14.3; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{16}H_{21}NNaO_3$, 298.1414; found: 298.1411.

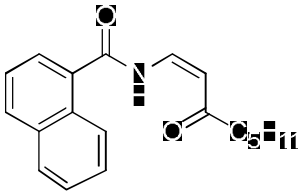


2-methoxy-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3da): Very pale yellow solid (60.4 mg, 0.219 mmol, 88%, Hex/EA = 8:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.98 (d, J = 10.4 Hz, 1 H), 8.24 (dd, J = 1.8, 7.8 Hz, 1 H), 7.76 – 7.48 (m, 2 H), 7.16 – 6.99 (m, 2 H), 5.61 (d, J = 8.7 Hz, 1 H), 4.19 (s, 3 H), 2.53 – 2.41 (m, 2 H), 1.75 – 1.60 (m, 2 H), 1.43 – 1.31 (m, 4 H), 1.01 – 0.86 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.9, 164.7, 158.8, 136.8, 134.7, 133.2, 121.4, 120.0, 111.9,

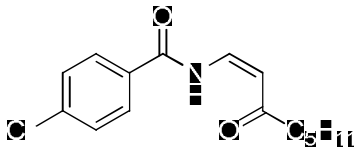
104.8, 56.1, 43.9, 31.8, 24.8, 22.8, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{16}H_{21}NNaO_3$, 298.1414; found: 298.1413.



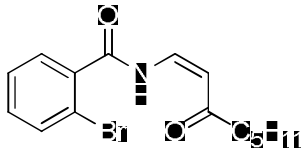
4-hydroxy-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ea): Yellow solid (54.4 mg, 0.208 mmol, 83%, Hex/EA = 5:2); ^1H NMR (300 MHz, $CDCl_3$) δ = 12.44 (d, *J* = 10.7 Hz, 1 H), 8.86 (br. s., 1 H), 7.92 (d, *J* = 8.7 Hz, 2 H), 7.72 (dd, *J* = 8.5, 10.7 Hz, 1 H), 7.12 - 6.99 (m, 2 H), 5.71 (d, *J* = 8.5 Hz, 1 H), 2.53 (t, *J* = 7.5 Hz, 2 H), 1.78 - 1.60 (m, 2 H), 1.43 - 1.30 (m, 4 H), 0.92 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 206.6, 165.5, 162.1, 139.6, 130.6, 123.4, 116.4, 104.2, 77.8, 76.9, 43.9, 31.7, 25.2, 22.7, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{15}H_{19}NNaO_3$, 284.1258; found: 284.1257.



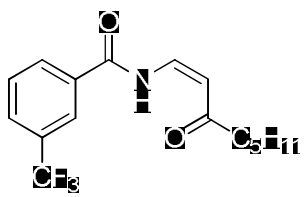
***N*-((*Z*)-3-oxooct-1-enyl)-1-naphthamide (3fa):** Pale yellow solid (56.0 mg, 0.190 mmol, 76%, Hex/EA = 12:1); ^1H NMR (300 MHz, $CDCl_3$) δ = 12.17 (d, *J* = 10.2 Hz, 1 H), 8.57 (d, *J* = 8.3 Hz, 1 H), 8.01 (d, *J* = 8.3 Hz, 1 H), 7.88 (dt, *J* = 0.8, 8.2 Hz, 2 H), 7.73 (t, *J* = 9.7 Hz, 1 H), 7.68 - 7.50 (m, 3 H), 5.67 (d, *J* = 8.7 Hz, 1 H), 2.49 (t, *J* = 7.4 Hz, 2 H), 1.72 - 1.56 (m, 2 H), 1.42 - 1.29 (m, 4 H), 0.97 - 0.86 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.5, 167.6, 137.6, 134.1, 132.8, 131.5, 130.8, 128.8, 128.0, 126.9, 126.8, 125.6, 124.9, 104.8, 43.7, 31.6, 24.4, 22.7, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{19}H_{21}NNaO_2$, 318.1465; found: 318.1465.



4-chloro-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ga): Yellow solid (49.9 mg, 0.178 mmol, 71%, Hex/EA = 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.58 (d, *J* = 9.8 Hz, 1 H), 8.08 – 7.85 (m, 2 H), 7.65 (dd, *J* = 10.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2 H), 5.68 (d, *J* = 8.5 Hz, 1 H), 2.52 (t, *J* = 7.5 Hz, 2 H), 1.67 (quin, *J* = 7.3 Hz, 2 H), 1.46 – 1.29 (m, 4 H), 0.99 – 0.88 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.1, 164.5, 139.8, 138.1, 130.7, 129.6, 129.6, 105.1, 43.9, 31.7, 24.5, 22.8, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{15}H_{18}ClNNaO_2$, 302.0920; found: 302.0918.

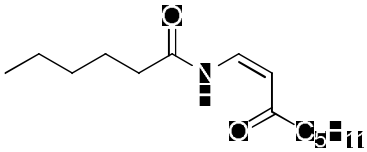


2-bromo-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ha): Orange oil (57.9 mg, 0.179 mmol, 71%, Hex/EA = 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.91 (d, *J* = 9.0 Hz, 1 H), 7.72 – 7.52 (m, 3 H), 7.50 – 7.31 (m, 2 H), 5.66 (d, *J* = 8.7 Hz, 1 H), 2.48 (t, *J* = 7.4 Hz, 2 H), 1.71 – 1.58 (m, 2 H), 1.40 – 1.26 (m, 4 H), 0.94 – 0.85 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.3, 166.4, 136.7, 136.0, 134.3, 132.6, 130.0, 128.0, 120.2, 105.5, 43.8, 31.7, 24.3, 22.7, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{15}H_{18}BrNNaO_2$, 346.0414; found: 346.0413.

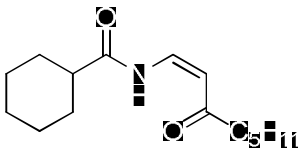


N-((*Z*)-3-oxooct-1-enyl)-3-(trifluoromethyl)benzamide (3ia):

Yellow oil (56.2 mg, 0.179 mmol, 72%, Hex/EA = 12:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.64 (d, *J* = 10.0 Hz, 1 H), 8.32 – 8.28 (m, 1 H), 8.12 (dd, *J* = 0.6, 7.9 Hz, 1 H), 7.85 (td, *J* = 0.7, 7.9 Hz, 1 H), 7.70 – 7.62 (m, 2 H), 5.71 (d, *J* = 8.5 Hz, 1 H), 2.56 – 2.49 (m, 2 H), 1.72 – 1.61 (m, 2 H), 1.38 – 1.29 (m, 4 H), 0.95 – 0.88 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.1, 164.2, 137.8, 133.3, 132.2, 131.8, 130.8, 129.8, 125.7, 122.0, 105.5, 43.9, 31.7, 24.5, 22.8, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{16}H_{18}F_3NNaO_2$, 336.1182; found: 336.1182.

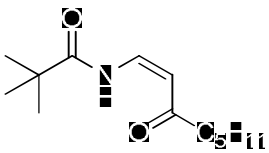


***N*-((*Z*)-3-oxooct-1-enyl)hexanamide (3ja):** Yellow oil (40.0 mg, 0.167 mmol, 67%, Hex/EA = 12:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.43 (d, *J* = 9.0 Hz, 1 H), 7.41 (dd, *J* = 8.6, 11.0 Hz, 1 H), 5.50 (d, *J* = 8.7 Hz, 1 H), 2.50 – 2.32 (m, 4 H), 1.75 – 1.56 (m, 4 H), 1.40 – 1.26 (m, 8 H), 0.93 – 0.85 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.4, 172.6, 137.4, 103.8, 43.7, 37.1, 31.7, 31.6, 25.0, 24.5, 22.8, 22.6, 14.2, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NNaO_2$, 262.1778; found: 262.1778.

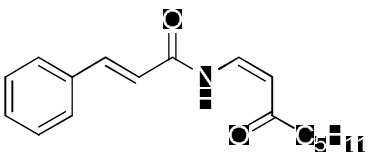


***N*-((*Z*)-3-oxooct-1-enyl)cyclohexanecarboxamide (3ka):** Yellow solid (45.4 mg, 0.181 mmol, 72%, Hex/EA = 12:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.54 (d, *J* = 9.6 Hz, 1 H), 7.42 (dd, *J* = 8.6, 11.0 Hz, 1 H), 5.51 (d, *J* = 8.5 Hz, 1 H), 2.44 (t, *J* = 7.4 Hz, 2 H), 2.26 (tt, *J* = 3.5, 11.5 Hz, 1 H), 1.94 (dd, *J* = 2.1, 12.8 Hz, 2 H), 1.81 (td, *J* = 2.7, 9.8 Hz, 2 H), 1.71 – 1.55 (m, 3 H), 1.55 – 1.39 (m, 3 H), 1.37

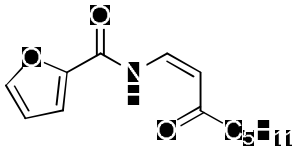
– 1.22 (m, 6 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.5, 175.4, 137.7, 103.9, 45.7, 43.6, 31.7, 29.4, 25.9, 25.8, 24.4, 22.7, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{15}H_{25}NNaO_2$, 274.1778; found: 274.1777.



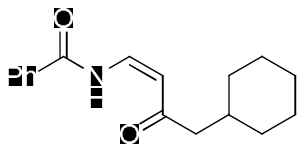
***N*-((*Z*))-3-oxooct-1-enyl)pivalamide (3la):** Yellow oil (38.8 mg, 0.172 mmol, 69%, Hex/EA = 20:1.1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.84 (d, 9 Hz, 1 H), 7.42 (dd, J = 8.6, 10.8 Hz, 1 H), 5.53 (d, J = 8.5 Hz, 1 H), 2.44 (t, J = 7.5 Hz, 2 H), 1.67 – 1.55 (m, 2 H), 1.38 – 1.25 (m, 13 H), 0.91 – 0.86 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.5, 178.1, 138.2, 104.0, 43.7, 31.7, 27.4, 24.5, 22.7, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{13}H_{23}NNaO_2$, 248.1621; found: 248.1621.



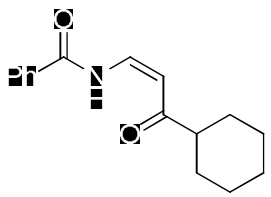
***N*-((*Z*)-3-oxooct-1-enyl)cinnamamide (3ma):** Yellow solid (47.8 mg, 0.176 mmol, 70%, Hex/EA = 8:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.75 (d, J = 10.4 Hz, 1 H), 7.88 – 7.72 (m, 1 H), 7.65 – 7.52 (m, 3 H), 7.48 – 7.38 (m, 3 H), 6.54 (d, J = 15.8 Hz, 1 H), 5.60 (d, J = 8.5 Hz, 1 H), 2.49 (t, J = 7.3 Hz, 2 H), 1.72 – 1.60 (m, 2 H), 1.45 – 1.31 (m, 4 H), 0.98 – 0.88 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.5, 164.6, 145.0, 137.8, 134.5, 130.9, 129.3, 128.6, 119.6, 104.4, 43.7, 31.7, 24.5, 22.8, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{17}H_{21}NNaO_2$, 294.1465; found: 294.1464.



N-((*Z*)-3-oxooct-1-enyl)furan-2-carboxamide (3na): Orange solid (38.1 mg, 0.162 mmol, 65%, Hex/EA = 6:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.34 (d, *J* = 9.8 Hz, 1 H), 7.67 – 7.50 (m, 2 H), 6.58 (dd, *J* = 1.7, 3.6 Hz, 1 H), 5.64 (d, *J* = 8.7 Hz, 1 H), 2.56 – 2.46 (m, 2 H), 1.77 – 1.60 (m, 2 H), 1.40 – 1.28 (m, 4 H), 0.95 – 0.89 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.4, 156.6, 146.9, 146.2, 136.7, 117.6, 113.0, 104.9, 43.8, 31.7, 24.4, 22.8, 14.2; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{13}H_{17}NNaO_3$, 258.1101; found: 258.1098.

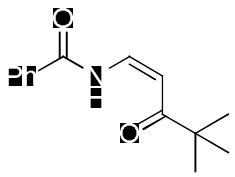


N-((*Z*)-4-cyclohexyl-3-oxobut-1-enyl)benzamide (3ab): Pale yellow oil (56.4 mg, 0.208 mmol, 83%, Hex/EA = 12:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.58 (d, *J* = 9.8 Hz, 1 H), 8.07 – 7.94 (m, 2 H), 7.71 – 7.42 (m, 4 H), 5.63 (d, *J* = 8.5 Hz, 1 H), 2.35 (d, *J* = 7.0 Hz, 2 H), 1.93 – 1.58 (m, 6 H), 1.36 – 0.89 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.5, 165.4, 138.1, 133.2, 132.2, 129.1, 128.1, 105.2, 51.6, 35.1, 33.5, 26.4, 26.4; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{17}H_{21}NNaO_2$, 294.1465; found: 294.1464.

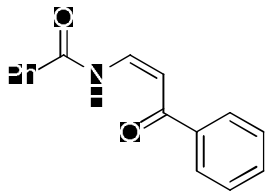


N-((*Z*)-3-cyclohexyl-3-oxoprop-1-enyl)benzamide (3ac): Colorless oil (52.0 mg, 0.202 mmol, 81%, Hex/EA = 15:1); ^{1}H NMR

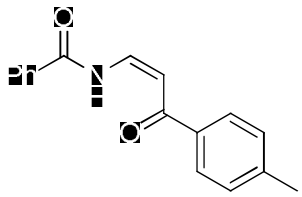
(300 MHz, $CDCl_3$) δ = 12.60 (d, *J* = 9.0 Hz, 1 H), 8.07 – 7.97 (m, 2 H), 7.71 (dd, *J* = 8.5, 10.7 Hz, 1 H), 7.63 – 7.47 (m, 3 H), 5.71 (d, *J* = 8.7 Hz, 1 H), 2.53 – 2.33 (m, 1 H), 1.97 – 1.78 (m, 4 H), 1.76 – 1.68 (m, 1 H), 1.44 – 1.26 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.7, 165.5, 138.9, 133.3, 132.4, 129.2, 128.2, 103.8, 51.4, 29.1, 26.2, 26.0; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{16}H_{19}NNaO_2$, 280.1308; found: 280.1308.



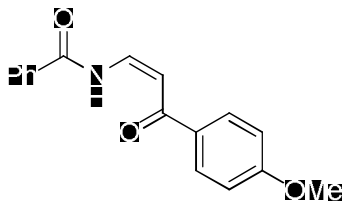
***N*-((*Z*)-4,4-dimethyl-3-oxopent-1-enyl)benzamide (3ad):** Yellow oil (52.9 mg, 0.229 mmol, 91%, Hex/EA = 11:1); ^1H NMR (300 MHz, $CDCl_3$) δ = 12.55 (d, *J* = 12 Hz, 1 H), 8.01 – 7.96 (m, 2 H), 7.73 (dd, *J* = 8.7, 10.7 Hz, 1 H), 7.60 – 7.45 (m, 3 H), 5.86 (d, *J* = 8.7 Hz, 1 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.8, 165.4, 139.2, 133.2, 132.3, 129.1, 128.1, 100.7, 43.5, 27.0; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{14}H_{17}NNaO_2$, 254.1151; found: 254.1152.



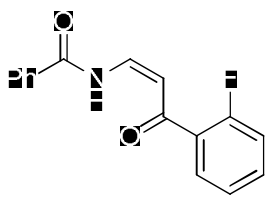
***N*-((*Z*)-3-oxo-3-phenylprop-1-enyl)benzamide (3ae):** White solid (37.4 mg, 0.149 mmol, 60%, Hex/EA = 10:1); ^1H NMR (499 MHz, $CDCl_3$) δ = 12.95 (d, *J* = 9.8 Hz, 1 H), 8.10 – 7.98 (m, 4 H), 7.96 (dd, *J* = 8.8, 10.8 Hz, 1 H), 7.68 – 7.44 (m, 5 H), 6.42 (d, *J* = 8.8 Hz, 1 H); The characterization data was identified with spectral comparison the literature data.[5]



N-((*Z*)-3-oxo-3-(p-tolyl)prop-1-enyl)benzamide (3af): Yellow solid (46.3 mg, 0.174 mmol, 70%, Hex/EA = 8:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.96 (d, *J* = 10.0 Hz, 1 H), 8.10 – 8.05 (m, 2 H), 7.97 – 7.88 (m, 3 H), 7.70 – 7.48 (m, 3 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 6.40 (d, *J* = 8.7 Hz, 1 H), 2.44 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.2, 165.6, 144.1, 140.1, 135.9, 133.4, 132.4, 129.7, 129.3, 128.3, 128.3, 101.2, 22.0; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{17}H_{15}NNaO_2$, 288.0995; found: 288.0995.

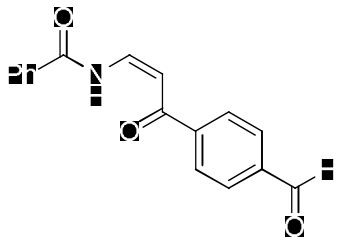


N-((*Z*)-3-(4-methoxyphenyl)-3-oxoprop-1-enyl)benzamide (3ag): White solid (42.2 mg, 0.150 mmol, 60%, Hex/EA = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 13.00 (br. s., 1 H), 8.12 – 7.97 (m, 4 H), 7.92 (dd, *J* = 8.7, 10.5 Hz, 1 H), 7.72 – 7.52 (m, 3 H), 7.14 – 6.94 (m, 2 H), 6.39 (d, *J* = 8.9 Hz, 1 H), 3.91 (s, 3 H); The characterization data was identified with spectral comparison the literature data.[5]



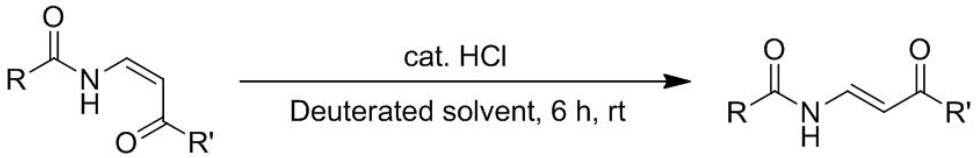
N-((*Z*)-3-(2-fluorophenyl)-3-oxoprop-1-enyl)benzamide (3ah): Yellow solid (47.9 mg, 0.178 mmol, 71%, Hex/EA = 7:1); ^{1}H NMR

(300 MHz, $CDCl_3$) δ = 12.80 (d, *J* = 10.0 Hz, 1 H), 8.09 – 8.04 (m, 2 H), 7.96 – 7.84 (m, 2 H), 7.67 – 7.47 (m, 4 H), 7.31 – 7.22 (m, 1 H), 7.15 (ddd, *J* = 0.9, 8.3, 11.3 Hz, 1 H), 6.37 (dd, *J* = 2.3, 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.3, 165.7, 161.5, 140.5, 134.6, 133.5, 132.3, 131.0, 129.3, 128.4, 127.3, 124.9, 117.1, 105.1; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{16}H_{12}FNNaO_2$, 292.0744; found: 292.0744.



***N*-((*Z*)-3-(4-formylphenyl)-3-oxoprop-1-enyl)benzamide (3ai):** White solid (42.8 mg, 0.153 mmol, 61%, Hex/EA = 7:2); ^1H NMR (300 MHz, $CDCl_3$) δ = 12.87 (d, *J* = 10.5 Hz, 1 H), 10.11 (s, 1 H), 8.29 – 7.93 (m, 7 H), 7.80 – 7.49 (m, 3 H), 6.40 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.4, 191.8, 165.5, 142.9, 141.6, 139.1, 133.6, 132.0, 130.2, 129.3, 128.7, 128.3, 100.9.; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{17}H_{13}NNaO_3$, 302.0788; found: 302.0787.

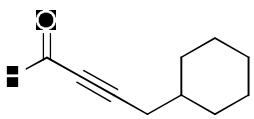
4. General procedure for isomerization of *Z*-enamide to *E*-enamide



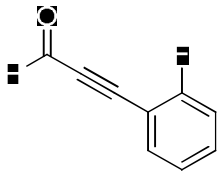
Z-enamide (0.125 mmol), 4 M HCl in dioxane (3.1 μL, 0.0125 mmol), and deuterated solvents (0.5 mL) were added into a 4-ml vial under the air condition. The reaction mixture was stirred for 6 h at

room temperature. NMR spectra of the crude reaction mixture were checked without further purification. The ratio of *Z*-enamide and *E*-enamide was determined by ^{1}H NMR without isolation of each enamides using significant difference of chemical shifts of H(NH) of each *Z*- and *E*-enamides.

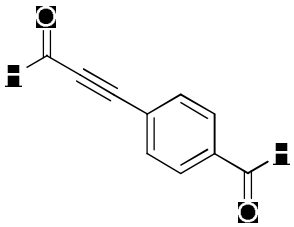
5. Preparation of propargyl aldehyde



4-Cyclohexyl-2-butynal (2b): THF (10 mL) was added to an Ar-filled Schlenk flask using micro-syringe then cooled to -78℃. 3-Cycohexyl-1-propyne (975 μL, 6.74 mmol) and 1.6M *n*-BuLi in hexane (4.4 mL, 7.08 mmol) were added to the flask in sequence. The reaction mixture was warmed to room temperature and stirred for 15 min. The mixture was re-cooled to -78℃ and DMF (1.05 mL) was added. The mixture was warmed to room temperature again and stirred for 1 h. After the reaction, the crude mixture was poured into an actively stirred 10% aq. KH_2PO_4 solution (50 mL) and diethyl ether (50 mL) mixture pre-cooled to 0℃. The organic layer was extracted with diethyl ether, washed with brine, dried using $MgSO_4$, and then concentrated in vacuo. Flash column chromatography was followed to isolate the desired aldehyde using Hex/Ether (20:1) solvent mixture as an eluent. Colorless oil (921.3 mg, 6.13 mmol, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.20 (t, *J* = 0.9 Hz, 1 H), 2.33 (dd, *J* = 0.8, 6.6 Hz, 2 H), 1.93 - 1.53 (m, 6 H), 1.37 - 0.98 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.6, 98.9, 83.0, 37.1, 33.0, 27.2, 26.3, 26.3; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{10}H_{14}NaO$, 173.0942; found: 173.0938.

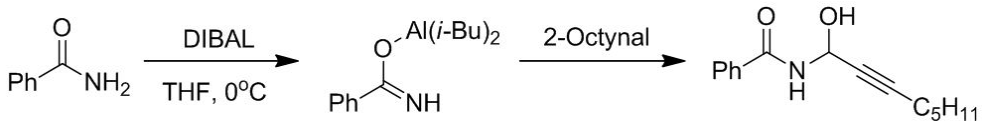


3-(2-Fluorophenyl)-2-propynal (2h): **3-(2-Fluorophenyl)prop-2-yn-1-ol** (29.03 mg, 1.93 mmol was oxidized to give **3-(2-fluorophenyl)-2-propynal (2h)** following the procedure as reported in the literature.[4] Yellow oil (96.7 mg, 0.65 mmol, 34%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 9.46 (s, 1 H), 7.62 – 7.56 (m, 1 H), 7.54 – 7.47 (m, 1 H), 7.23 – 7.19 (m, 1 H), 7.16 (t, *J* = 9.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.6, 163.9, 135.0, 133.6, 124.7, 116.2, 108.5, 92.7, 88.3; HRMS-ESI (m/z) $[2M+Na]^+$ calcd for $C_{18}H_{10}F_2NaO_2$, 319.0542; found: 319.0547.



4-(3-Oxo-1-propyn-1-yl)benzaldehyde (2i): **4-(3-Hydroxy-1-propyn-1-yl)benzaldehyde** (82.2 mg, 0.51 mmol) was oxidized to give **4-(3-oxo-1-propyn-1-yl)benzaldehyde (2i)** by the procedure reported in the literature.[4] White solid (58.5 mg, 0.37 mmol, 73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.09 (s, 1 H), 9.48 (s, 1 H), 8.10 – 7.88 (m, 2 H), 7.88 – 7.70 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.4, 176.7, 137.8, 134.0, 130.0, 125.6, 92.8, 90.4; HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{10}H_7O_2$, 159.0441; found: 159.0446.

6. Preparation of hemiaminal 5



The procedure was same as depicted in the literature.[6] Benzamide (0.121g, 1.0mmol) was dissolved in dry THF under Ar atmosphere. The mixture was stirred for 30 min at 0℃. 2-Octynal was added to the mixture and stirred for 20 h. After the reaction, ethyl acetate was added for dilution and then water was added to quench the reaction mixture. The organic layer was extracted with ethyl acetate and the layer was washed with brine. The solution was dried with $MgSO_4$, filtered, and concentrated in vacuo. Hemiaminal **5**, (***N*-(1-hydroxyoct-2-yn-1-yl)benzamide**), was isolated with flash column chromatography using Hex/EA (3:1) solvent mixture as an eluent. White solid (41.9 mg, 0.17 mmol, 17%); ^{1}H NMR (300MHz, THF-d_8) δ = 8.50 (d, J = 8.5 Hz, 1 H), 8.05 - 7.83 (m, 2 H), 7.60 - 7.29 (m, 3 H), 6.38 - 6.20 (m, 1 H), 5.49 (d, J = 5.3 Hz, 1 H), 2.24 (dt, J = 1.9, 7.1 Hz, 2 H), 1.68 - 1.28 (m, 6 H), 1.09 - 0.81 (m, 3 H); ^{13}C NMR (75MHz, THF-d_8) δ = 166.9, 136.2, 132.6, 129.5, 129.0, 83.9, 80.9, 65.9, 32.6, 29.8, 23.7, 19.8, 14.9; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{15}H_{19}NNaO_2$, 268.1308; found : 268.1309.

Reference of Experimental Section

1) Calderone, J. A.; Santos, W. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 4154.

2) Bowling, N. P.; Burrmann, N. J.; Halter, R. J.; Hodges, J. A.; McMahon, R. J. *J. Org. Chem.* **2010**, *75*, 6382.

3) Lee, K. Y.; Lee, M. J.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 5043.

4) Nowak-Król, A.; Koszarna, B.; Yoo, S. Y.; Chromiński, J.; Węcławski, M. K.; Lee C.-H.; Gryko, D. T. *J. Org. Chem.* **2011**, *76*, 2627.

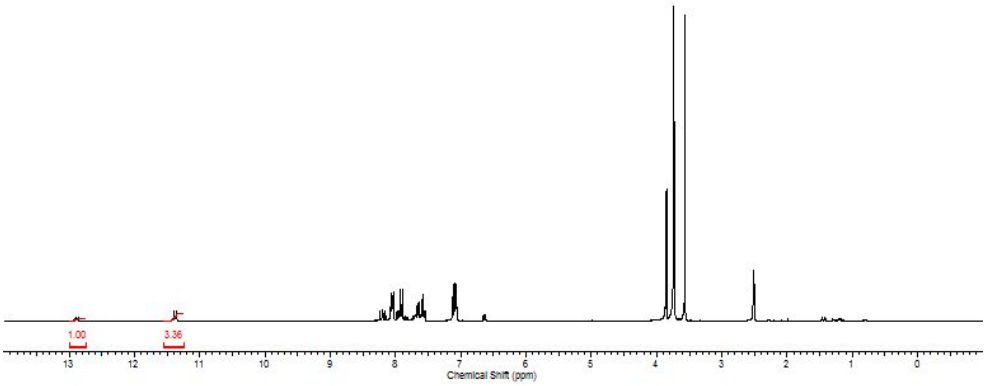
5) Panda, N.; Mothkuri, R. *J. Org. Chem.* **2012**, *77*, 9407.

6) Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665.

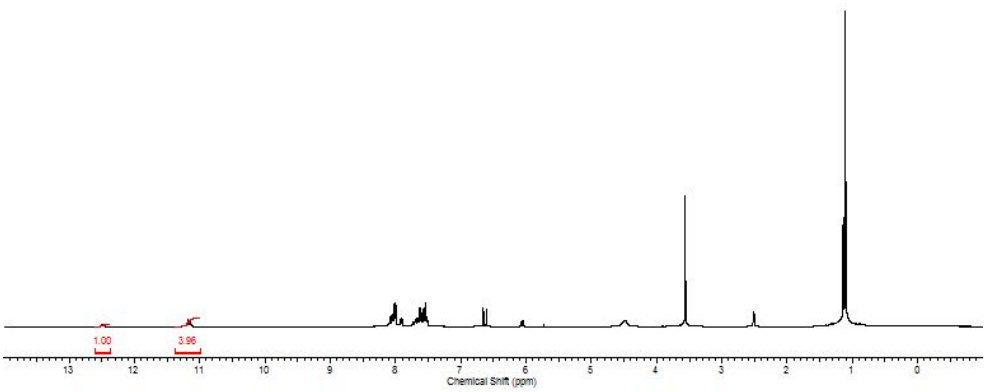
Supporting Information

1. ^{1}H NMR data of the isomerization reactions (Table 3)

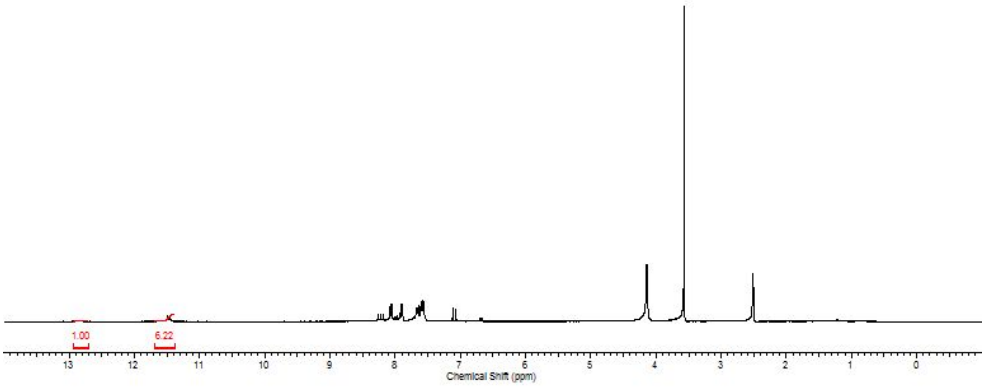
Entry 1 (DMSO-d_6)



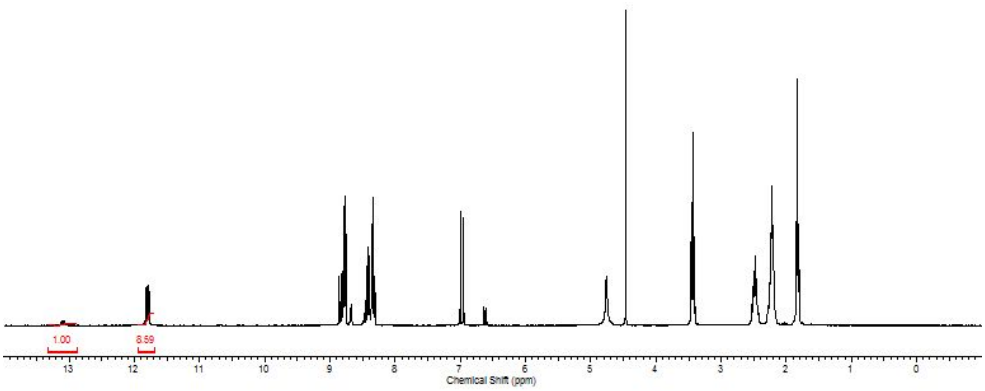
Entry 2 (DMSO-d_6)



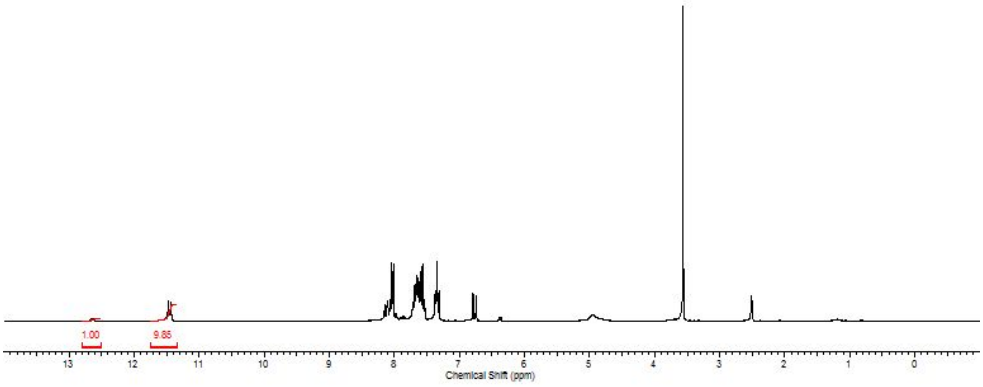
Entry 3 (DMSO-d_6)



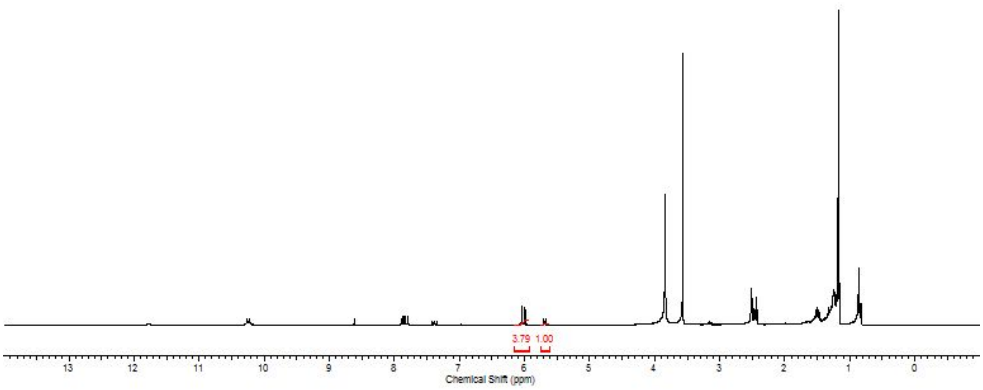
Entry 4 (DMSO-d_6)



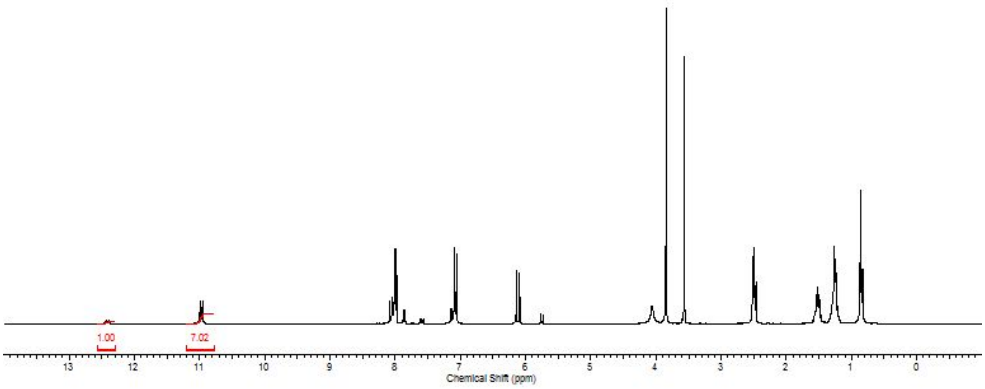
Entry 5 (DMSO-d_6)



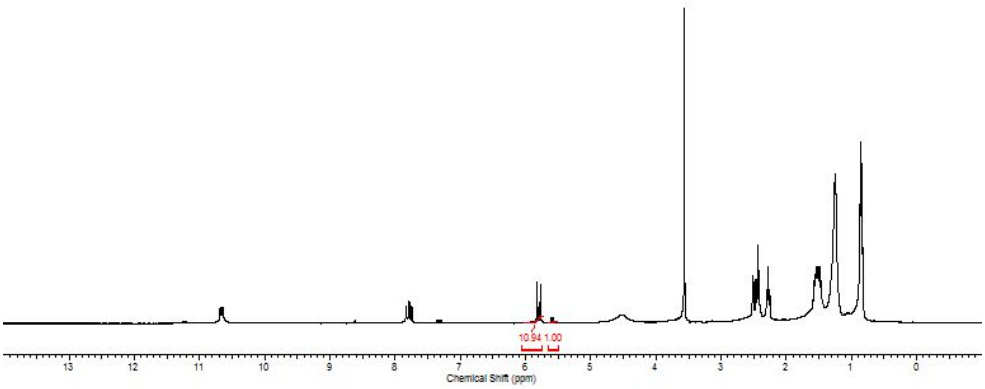
Entry 6 (DMSO-d_6)



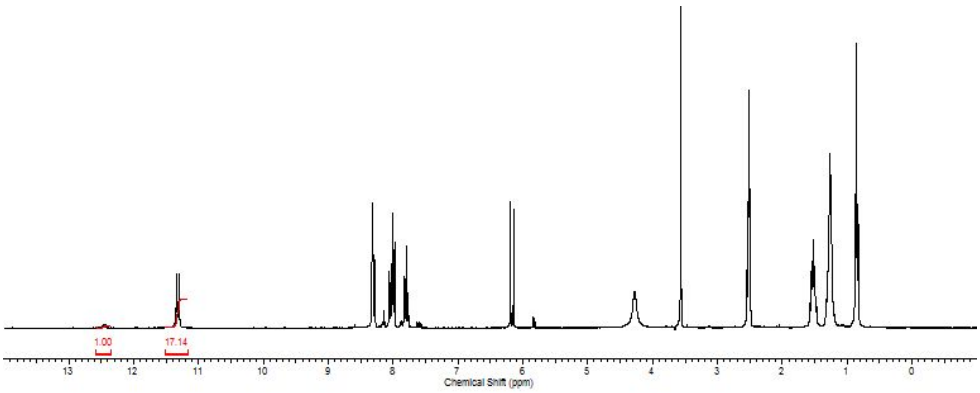
Entry 7 (DMSO-d_6)



Entry 8 (DMSO-d_6)



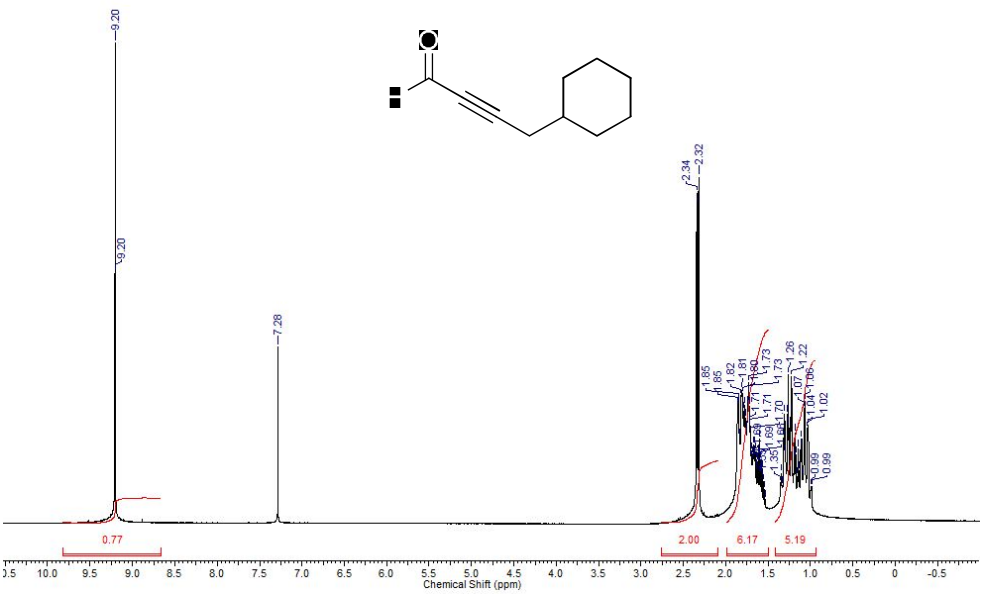
Entry 9 (DMSO-d_6)



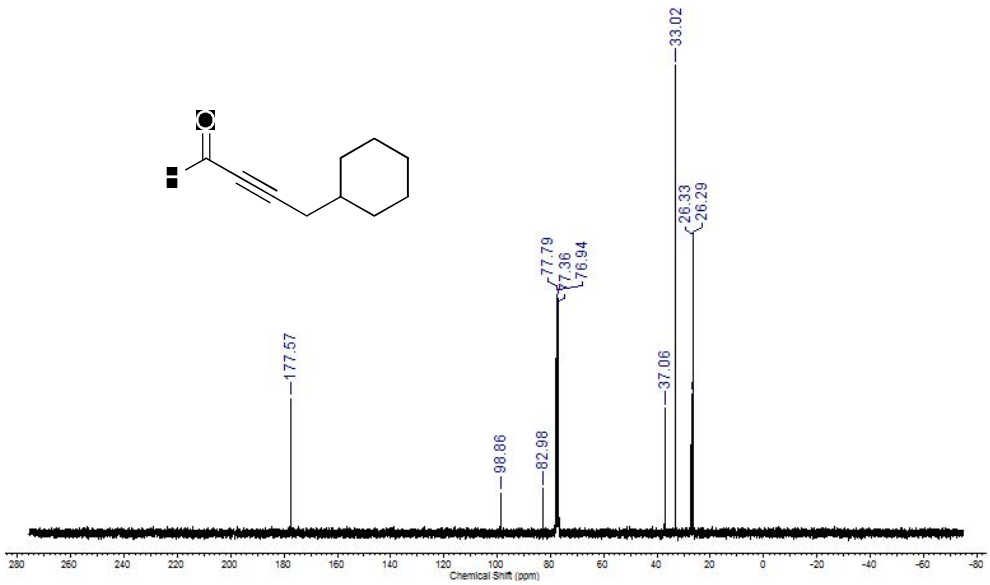
2. ^{1}H NMR and ^{13}C NMR spectra

-Cyclohexylbut-2-ynal (2b)

^{1}H NMR spectrum of **2b** ($CDCl_3$)

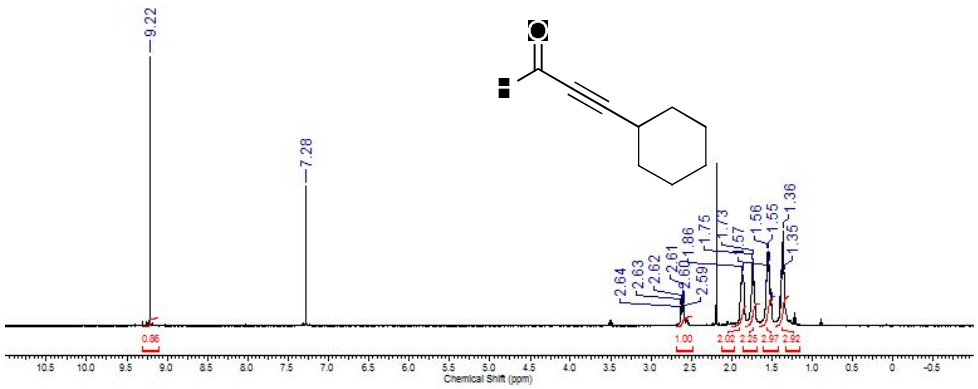


^{13}C NMR spectrum of **2b** ($CDCl_3$)



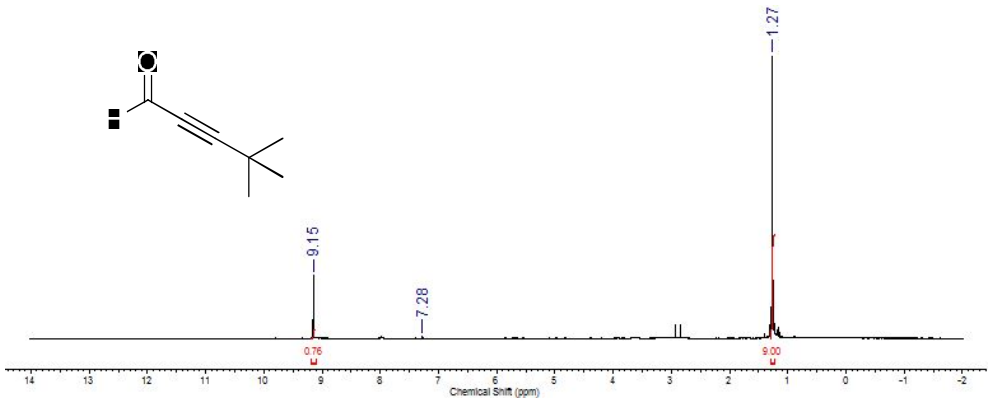
3-Cyclohexylpropioaldehyde (2c)

^{1}H NMR spectrum of **2c** ($CDCl_3$)



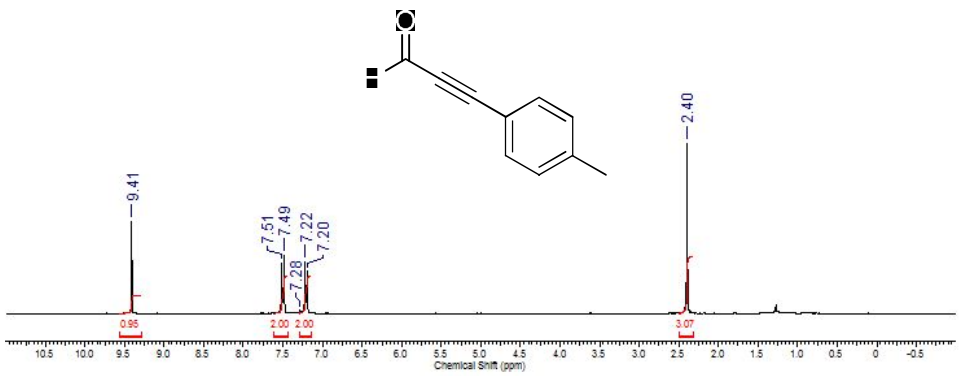
4,4-Dimethylpent-2-ynal (2d)

^{1}H NMR spectrum of **2d** ($CDCl_3$)



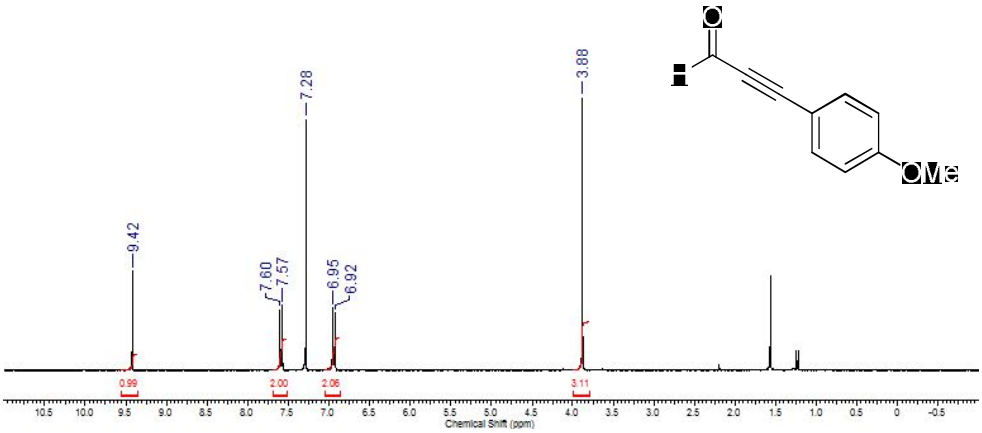
3-(*p*-Tolyl)propioaldehyde (2f)

^{1}H NMR spectrum of **2f** ($CDCl_3$)



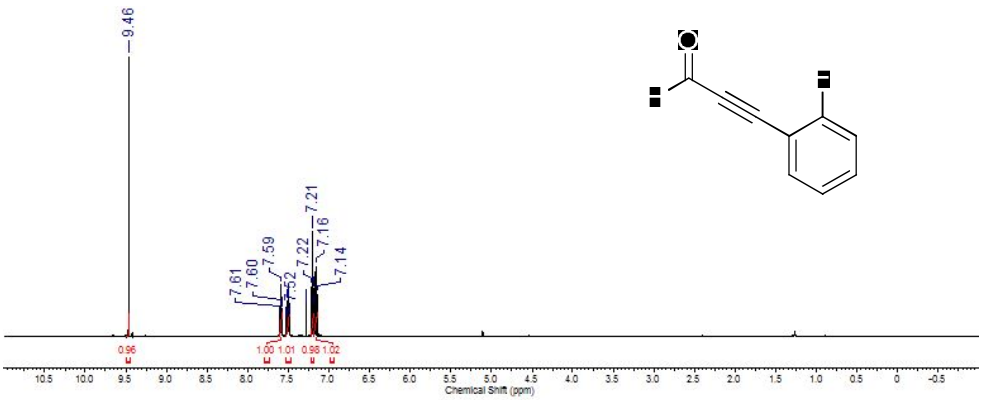
3-(4-Methoxyphenyl)propioaldehyde (2g)

^{1}H NMR spectrum of **2g** ($CDCl_3$)

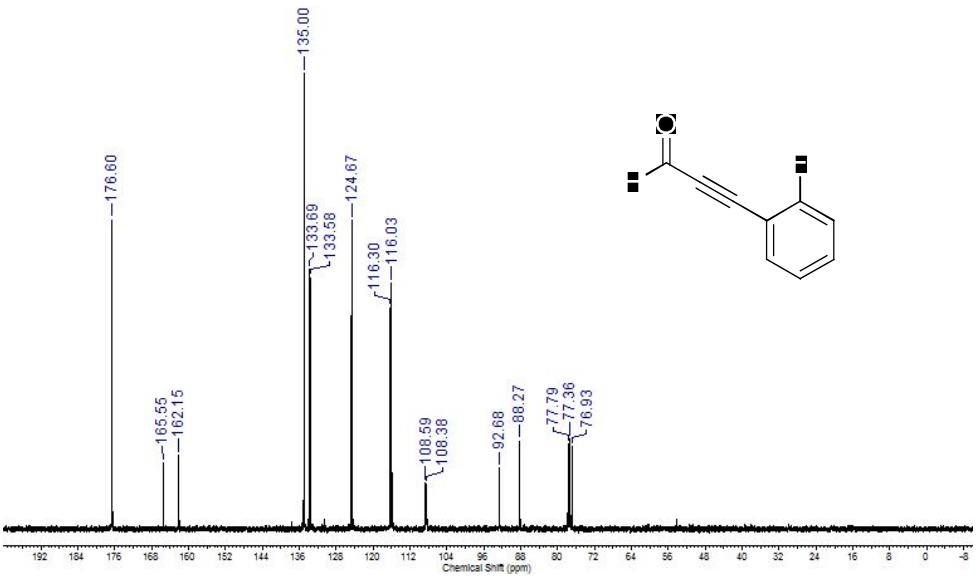


3-(2-Fluorophenyl)propioaldehyde (2h)

^{1}H NMR spectrum of **2h** ($CDCl_3$)

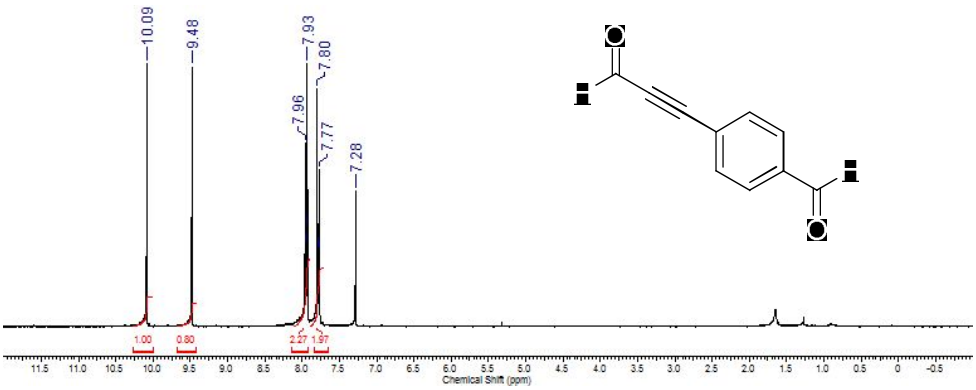


^{13}C NMR spectrum of **2h** ($CDCl_3$)

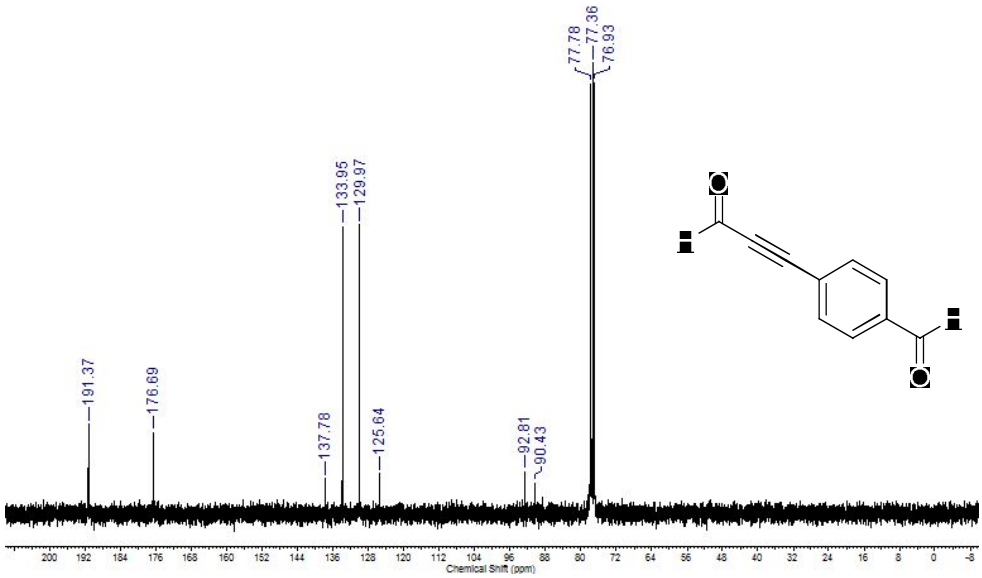


4-(3-Oxoprop-1-ynyl)benzaldehyde (2i)

^{1}H NMR spectrum of **2i** ($CDCl_3$)

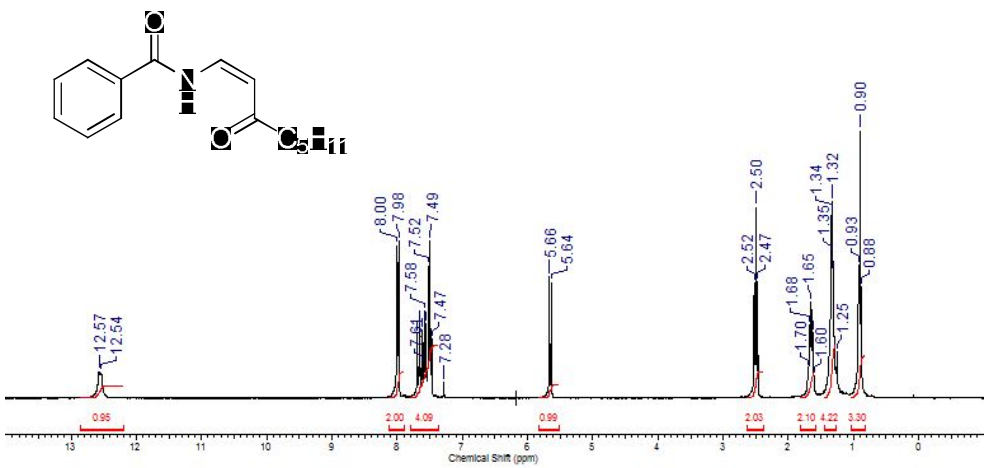


^{13}C NMR spectrum of **2i** ($CDCl_3$)

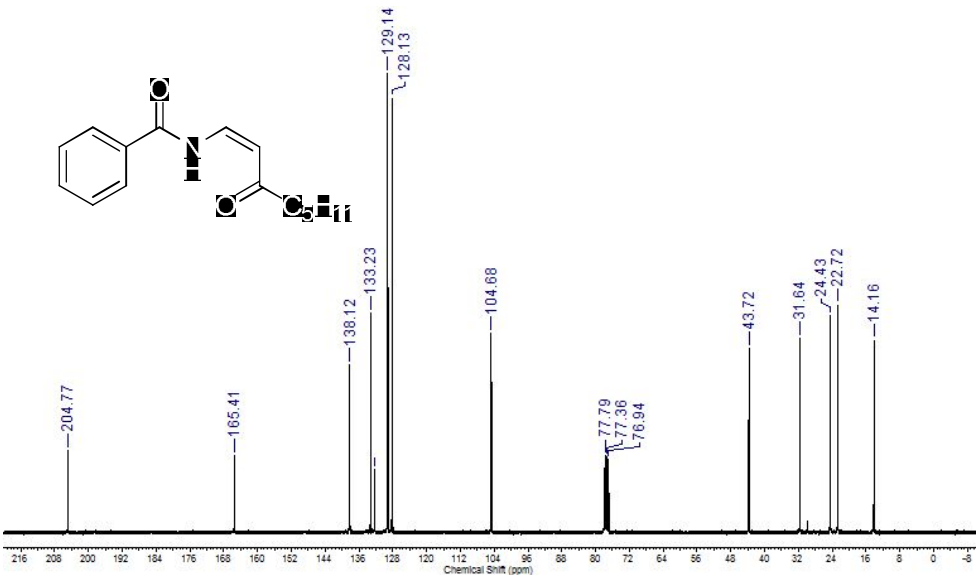


N-((*Z*)-3-oxooct-1-enyl)benzamide (3aa)

^{1}H NMR spectrum of **3aa** ($CDCl_3$)

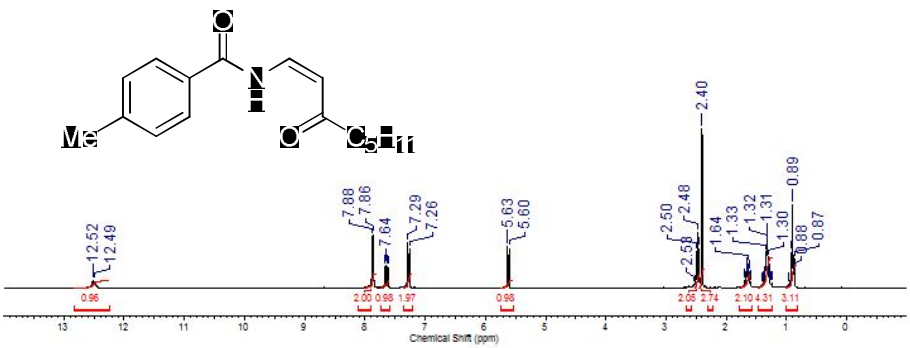


^{13}C NMR spectrum of **3aa** ($CDCl_3$)

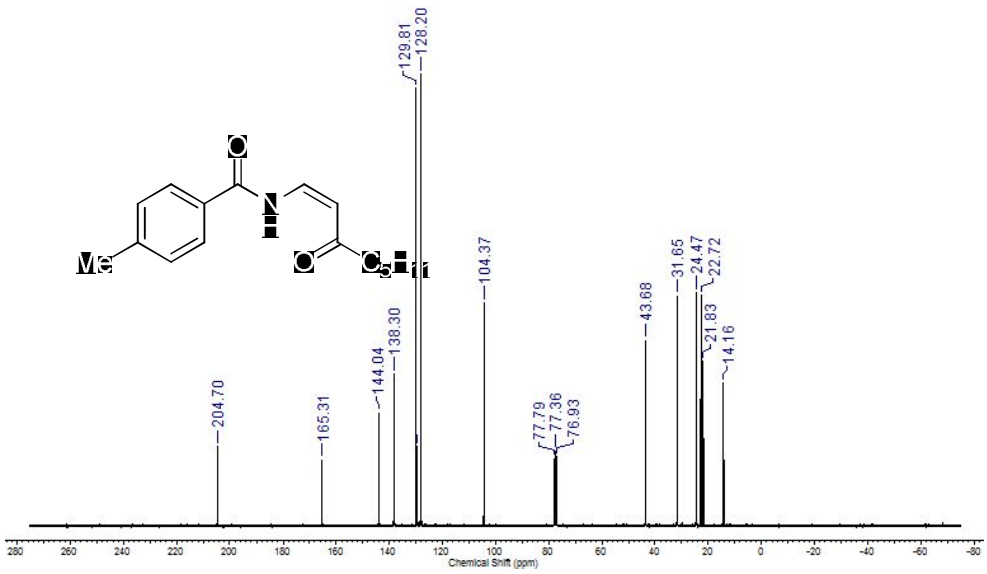


4-methyl-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ba)

^{1}H NMR spectrum of **3ba** ($CDCl_3$)

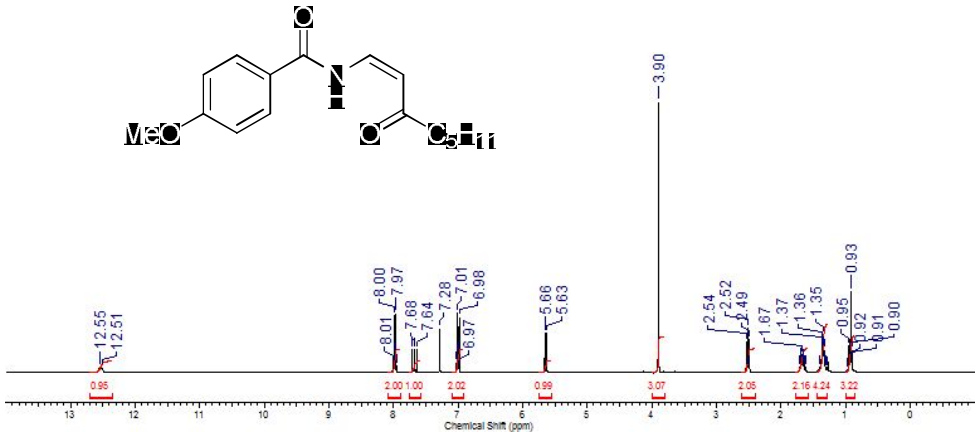


^{13}C NMR spectrum of **3ba** ($CDCl_3$)

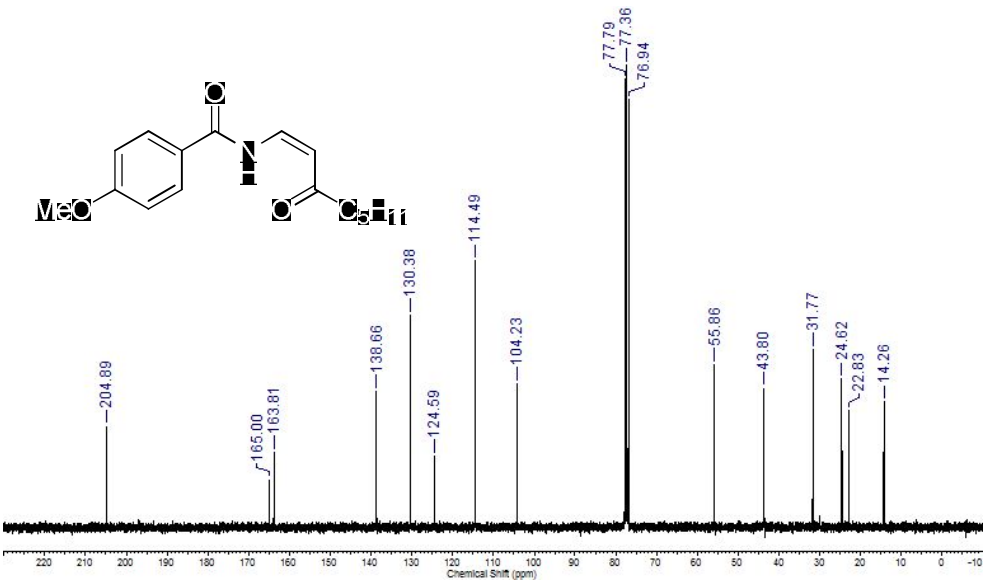


4-methoxy-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ca)

^{1}H NMR spectrum of **3ca** ($CDCl_3$)

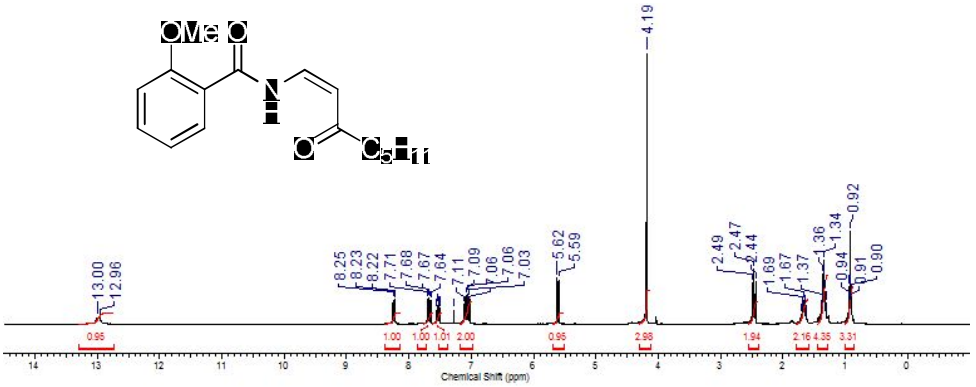


^{13}C NMR spectrum of **3ca** ($CDCl_3$)

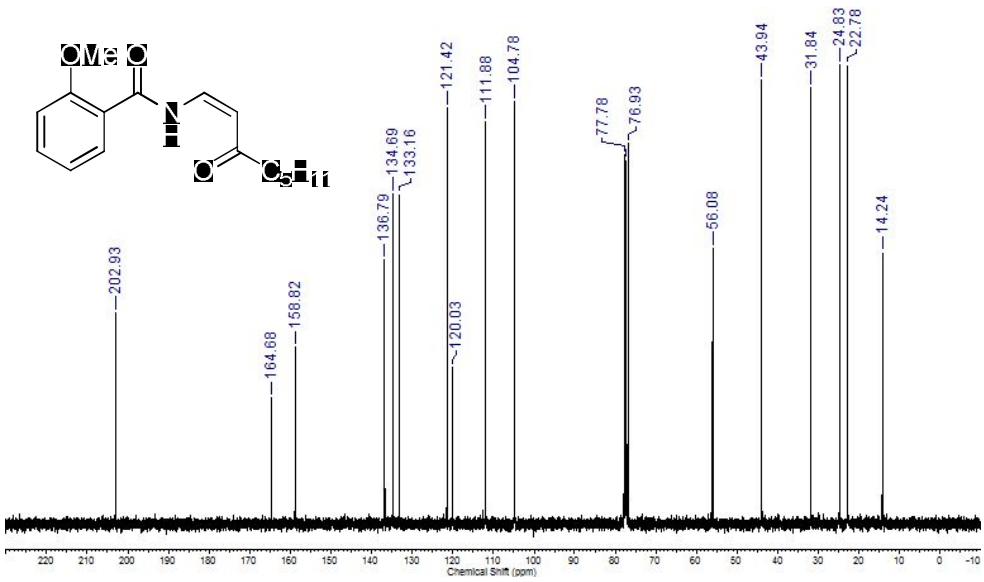


2-methoxy-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3da)

^{1}H NMR spectrum of **3da** ($CDCl_3$)

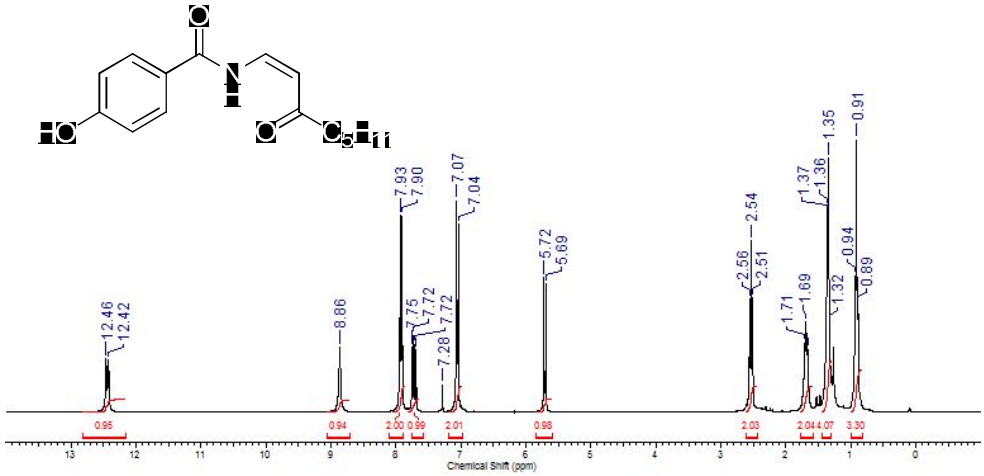


^{13}C NMR spectrum of **3da** ($CDCl_3$)

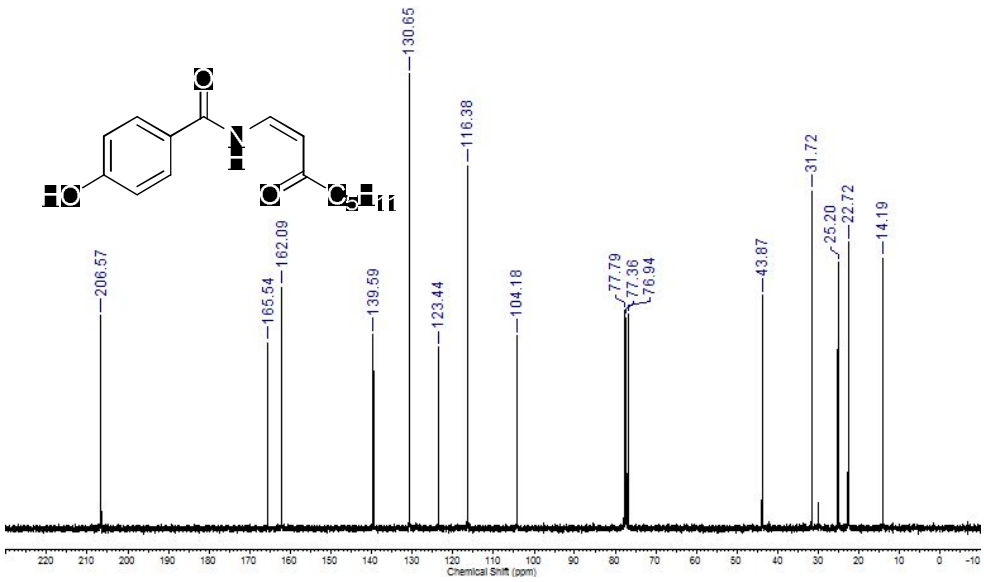


4-hydroxy-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ea)

^{1}H NMR spectrum of **3ea** ($CDCl_3$)

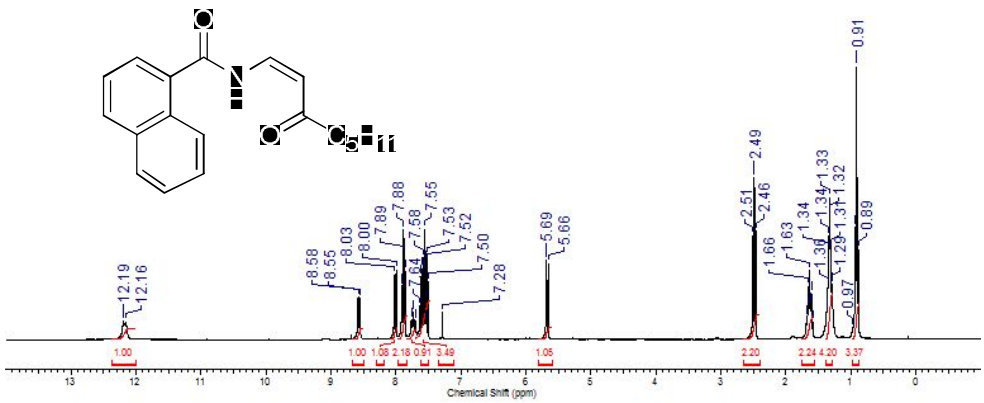


^{13}C NMR spectrum of **3ea** ($CDCl_3$)

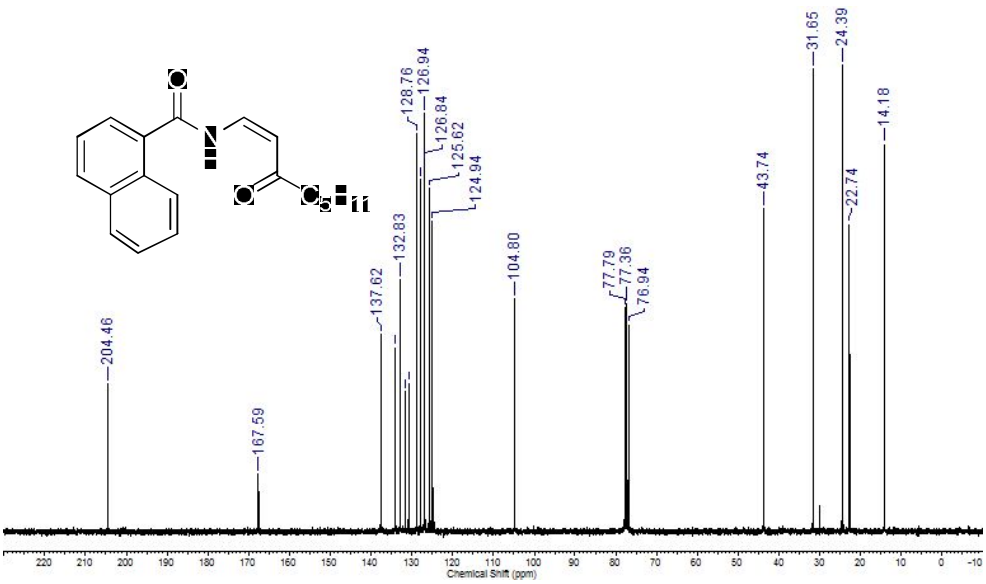


N-((*Z*)-3-oxooct-1-enyl)-1-naphthamide (3fa)

^{1}H NMR spectrum of **3fa** ($CDCl_3$)

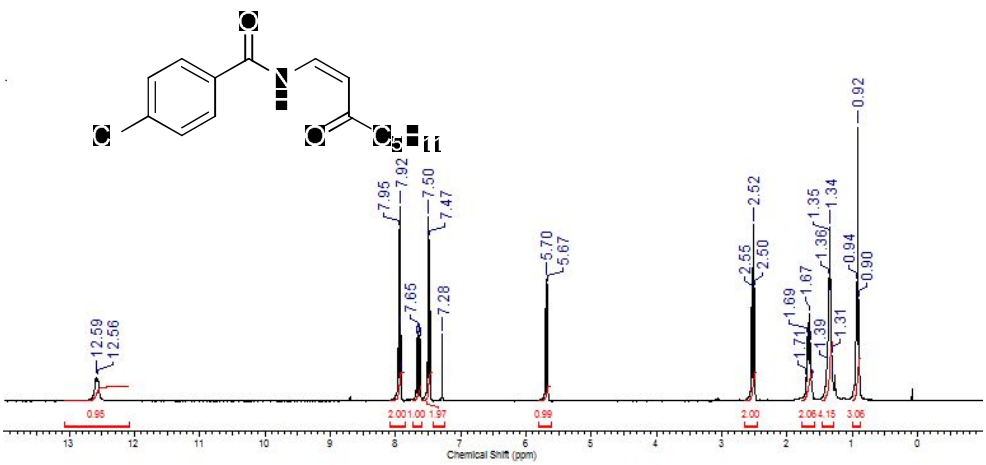


^{13}C NMR spectrum of **3fa** ($CDCl_3$)

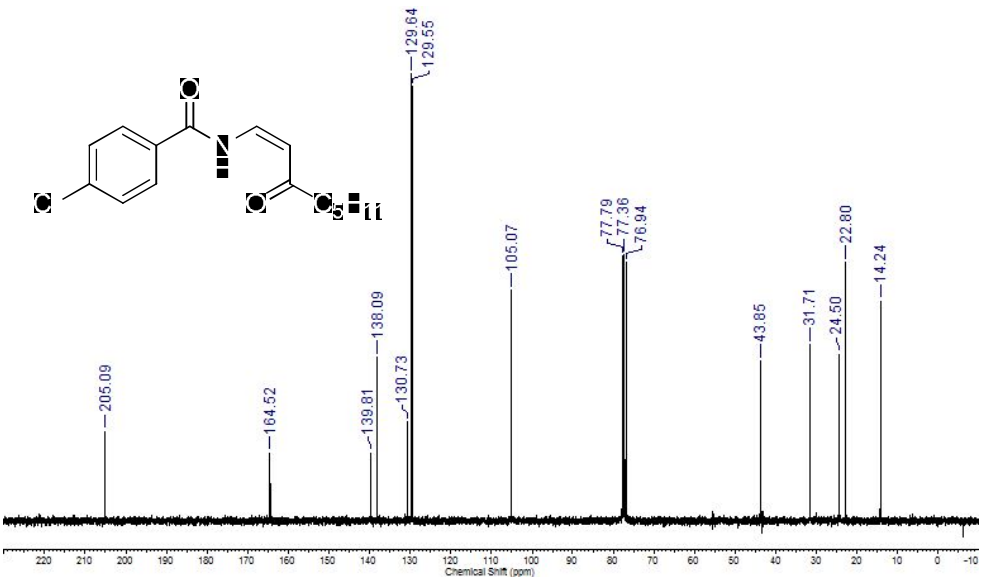


4-chloro-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ga)

^{1}H NMR spectrum of **3ga** ($CDCl_3$)

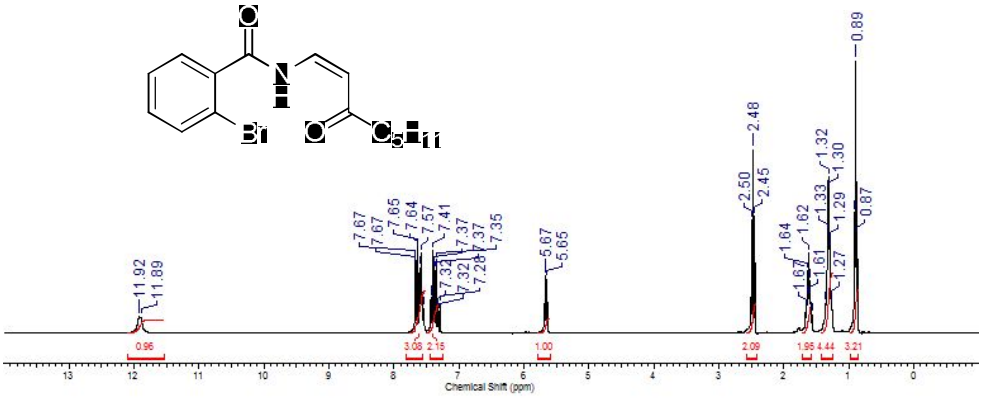


^{13}C NMR spectrum of **3ga** ($CDCl_3$)

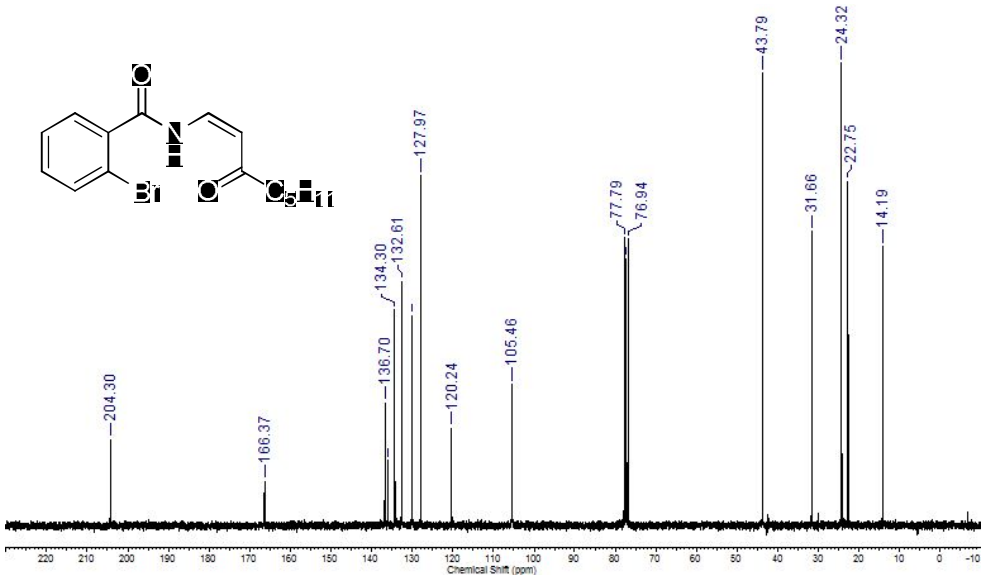


2-bromo-*N*-((*Z*)-3-oxooct-1-enyl)benzamide (3ha)

^{1}H NMR spectrum of **3ha** ($CDCl_3$)

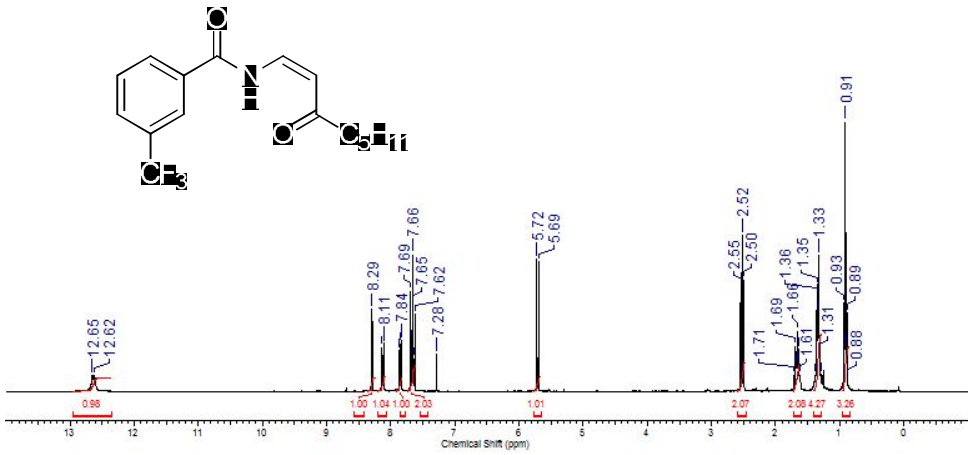


^{13}C NMR spectrum of **3ha** ($CDCl_3$)

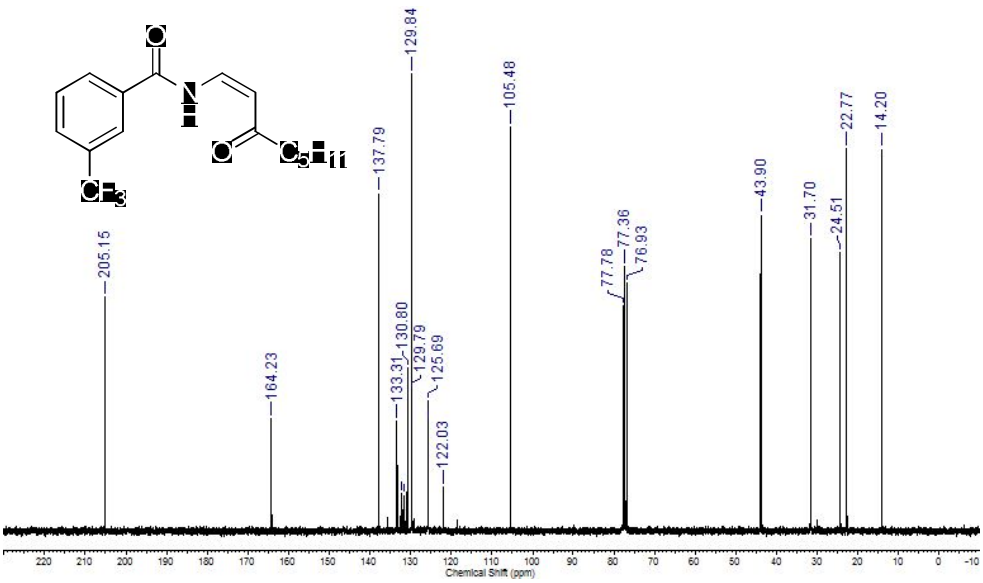


N-((*Z*)-3-oxooct-1-enyl)-3-(trifluoromethyl)benzamide (3ia)

^{1}H NMR spectrum of **3ia** ($CDCl_3$)

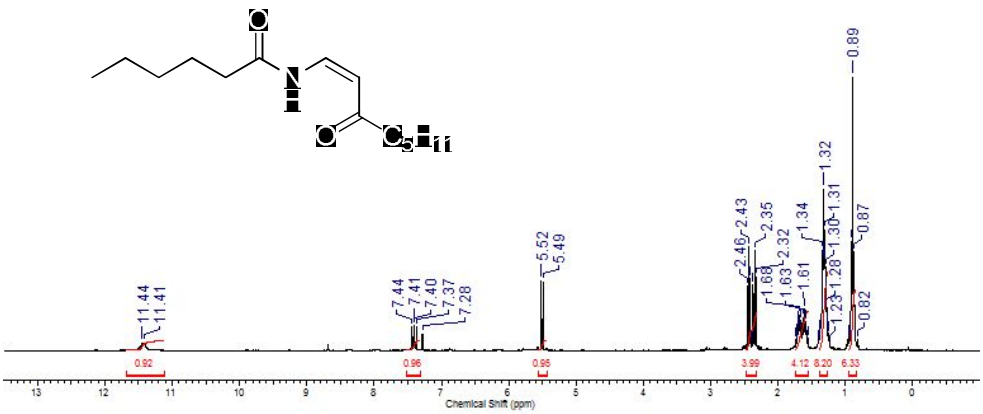


^{13}C NMR spectrum of **3ia** ($CDCl_3$)

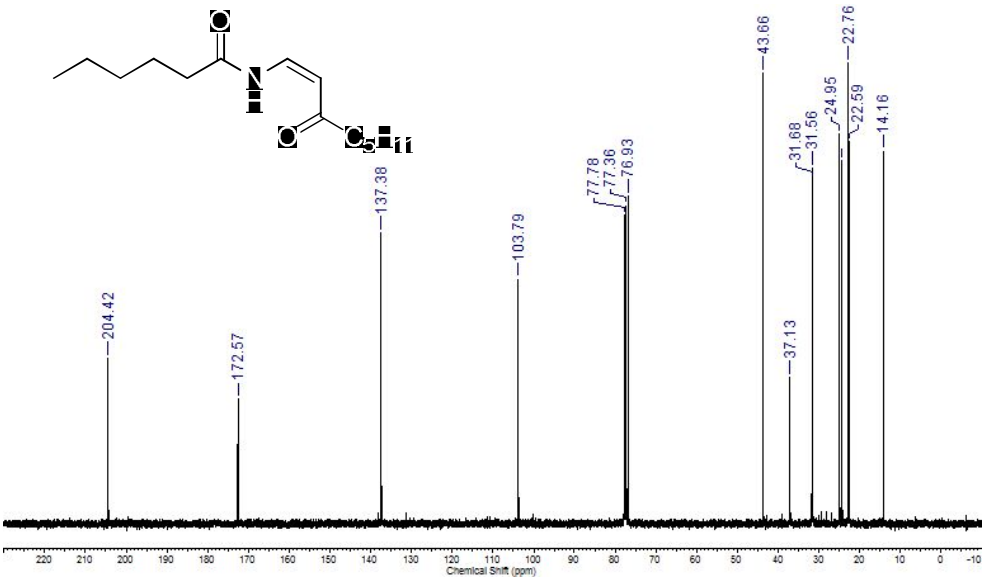


N-((*Z*)-3-oxooct-1-enyl)hexanamide (3ja)

^{1}H NMR spectrum of **3ja** ($CDCl_3$)

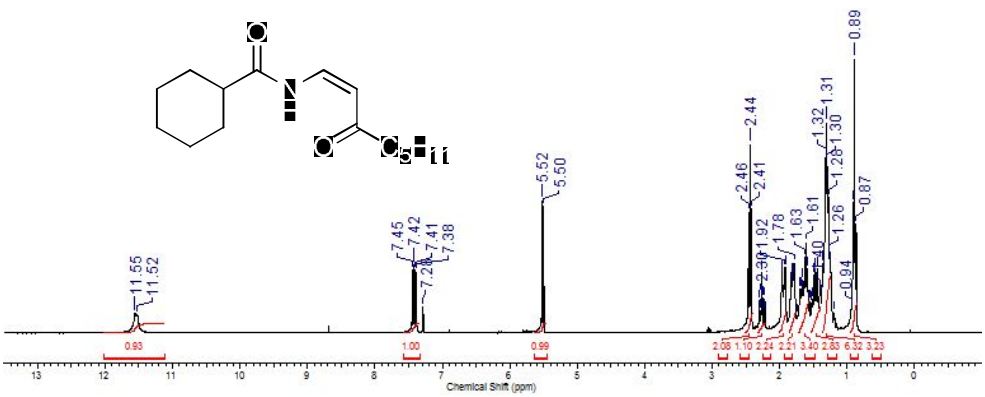


^{13}C NMR spectrum of **3ja** ($CDCl_3$)

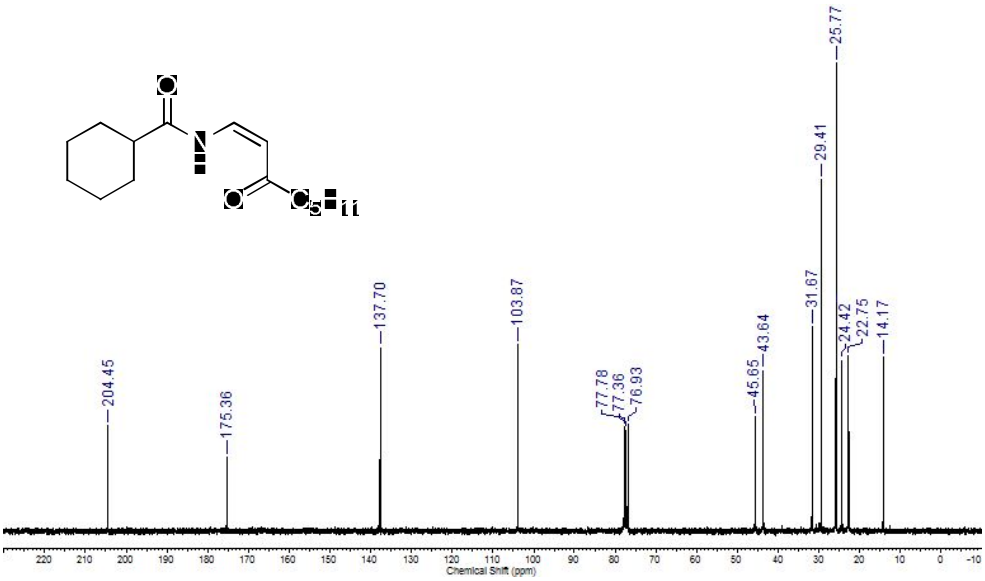


N-((*Z*)-3-oxooct-1-enyl)cyclohexanecarboxamide (3ka)

^{1}H NMR spectrum of **3ka** ($CDCl_3$)

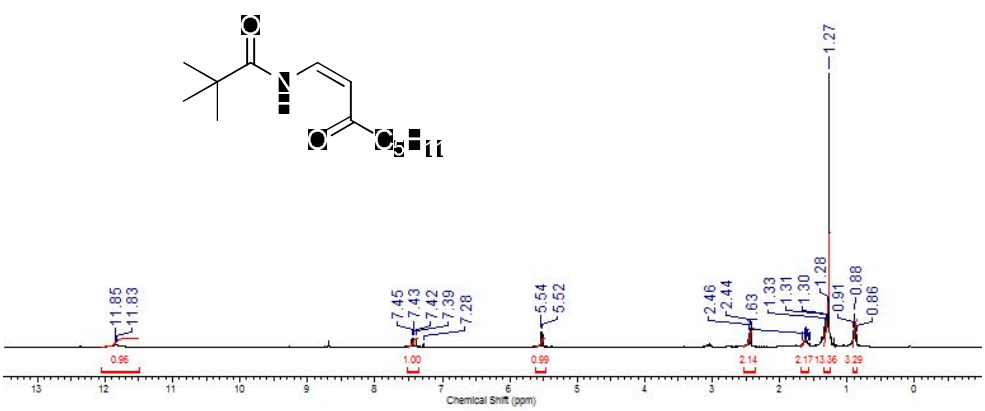


^{13}C NMR spectrum of **3ka** ($CDCl_3$)

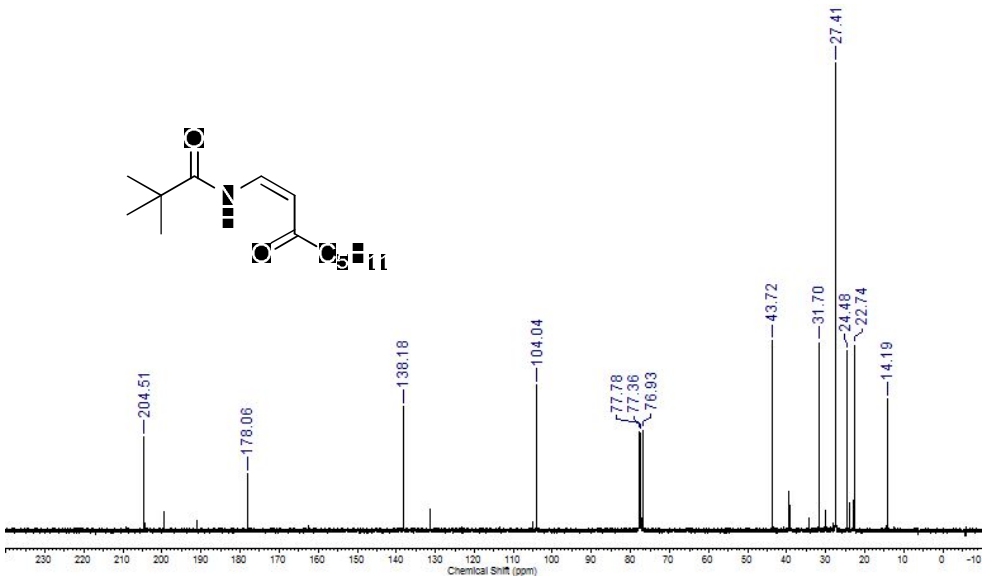


N-((*Z*))-3-oxooct-1-enyl)pivalamide (3la)

^{1}H NMR spectrum of **3la** ($CDCl_3$)

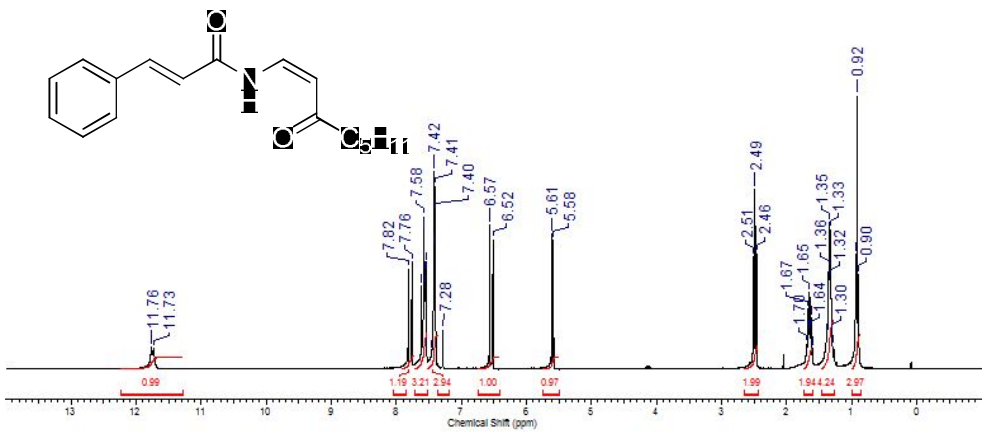


^{13}C NMR spectrum of **3la** ($CDCl_3$)

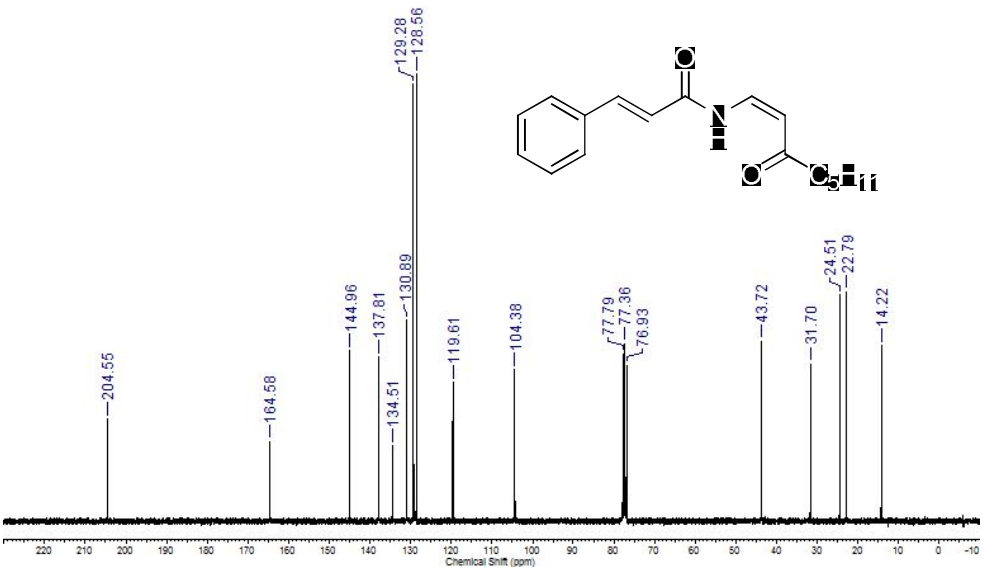


N-((*Z*)-3-oxooct-1-enyl)cinnamamide (3ma)

^{1}H NMR spectrum of **3ma** ($CDCl_3$)

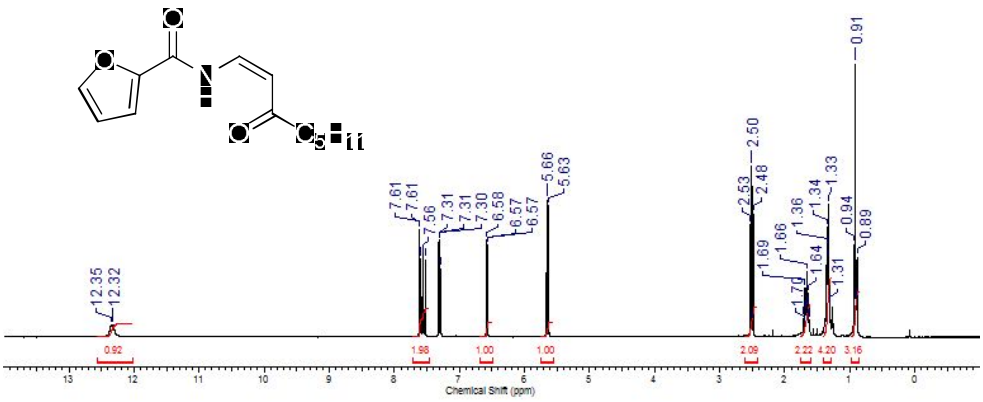


^{13}C NMR spectrum of **3ma** ($CDCl_3$)

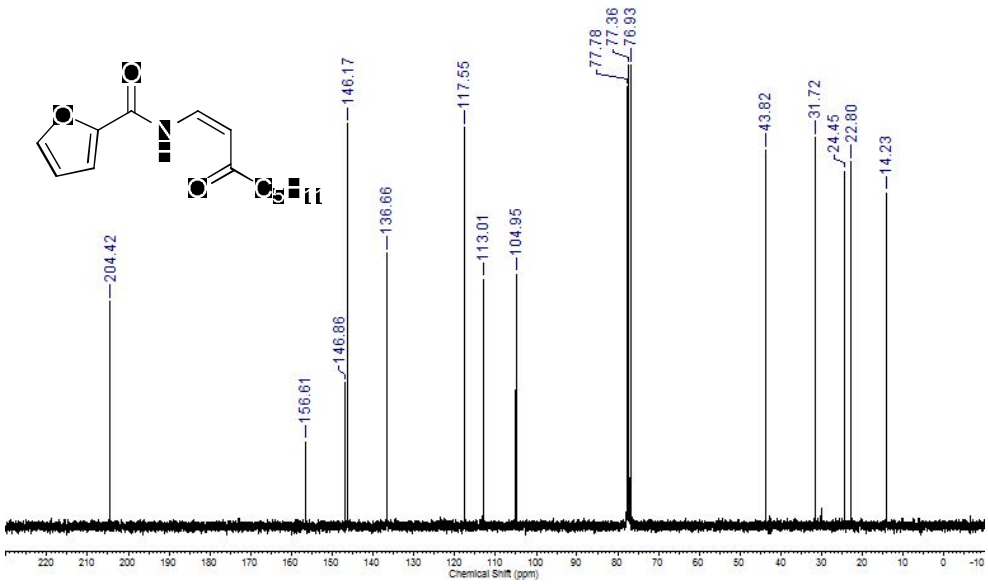


N-((*Z*)-3-oxooct-1-enyl)furan-2-carboxamide (3na)

^{1}H NMR spectrum of **3na** ($CDCl_3$)

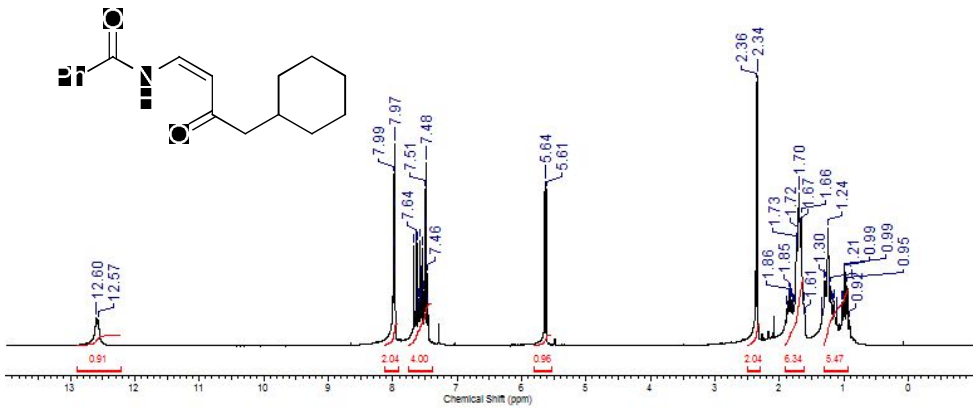


^{13}C NMR spectrum of **3na** ($CDCl_3$)

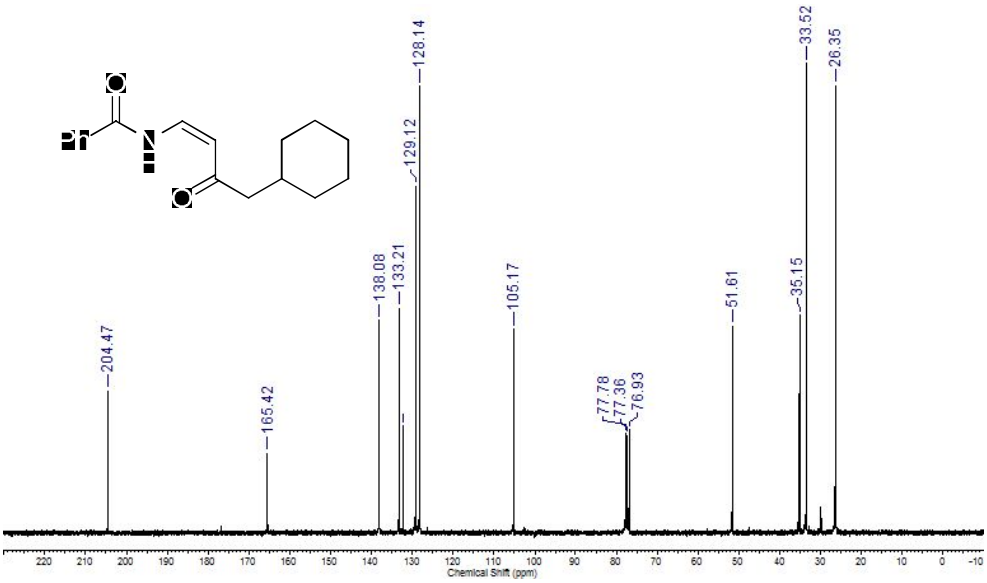


N-((*Z*)-4-cyclohexyl-3-oxobut-1-enyl)benzamide (3ab)

^{1}H NMR spectrum of **3ab** ($CDCl_3$)

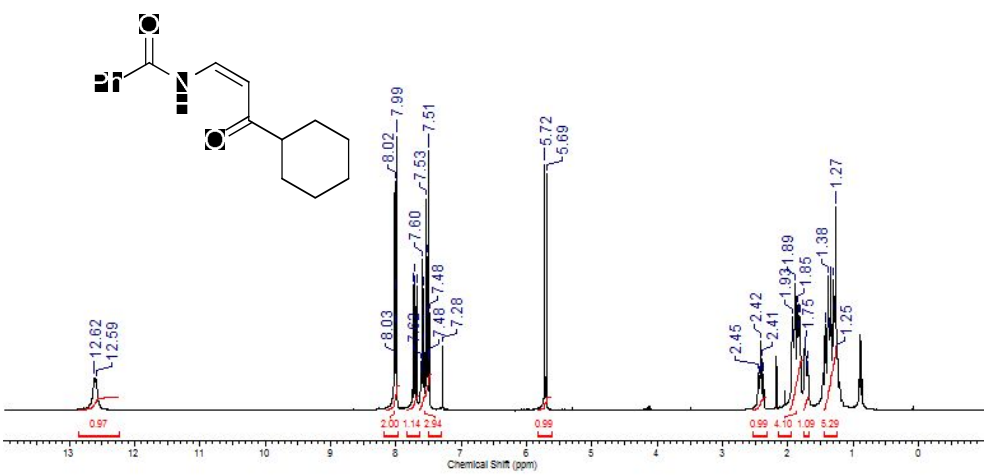


^{13}C NMR spectrum of **3ab** ($CDCl_3$)

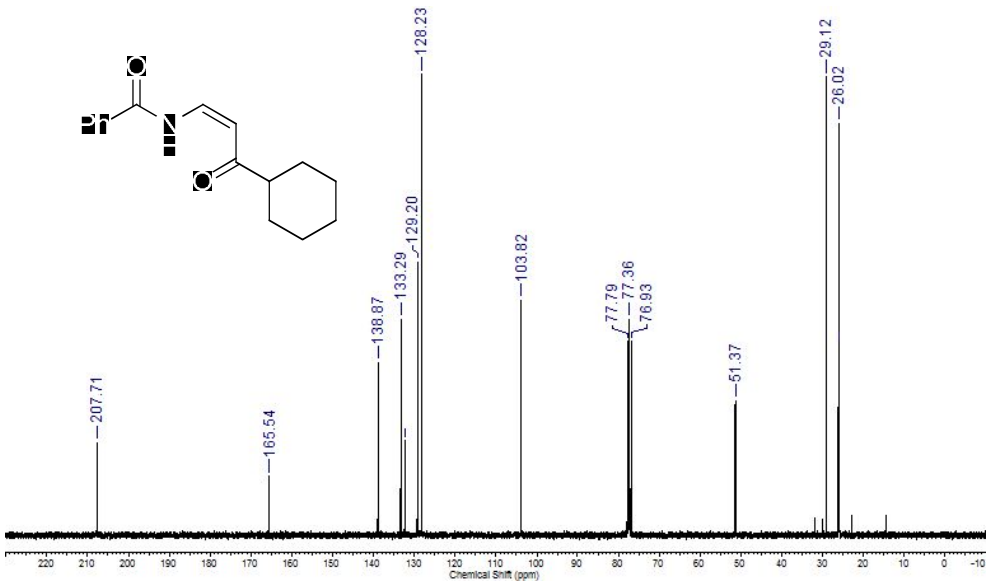


N-((*Z*)-3-cyclohexyl-3-oxoprop-1-enyl)benzamide (3ac)

^{1}H NMR spectrum of **3ac** ($CDCl_3$)

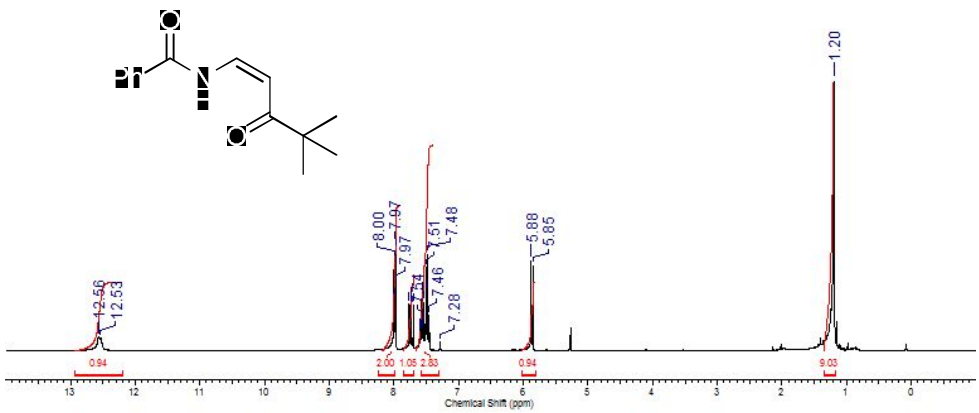


^{13}C NMR spectrum of **3ac** ($CDCl_3$)

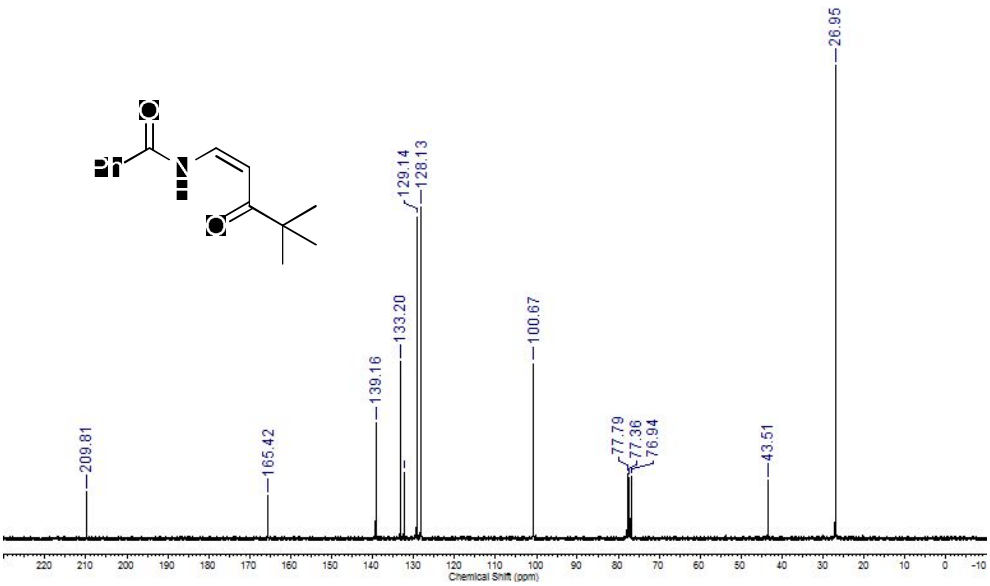


N-((*Z*)-4,4-dimethyl-3-oxopent-1-enyl)benzamide (3ad)

^{1}H NMR spectrum of **3ad** ($CDCl_3$)

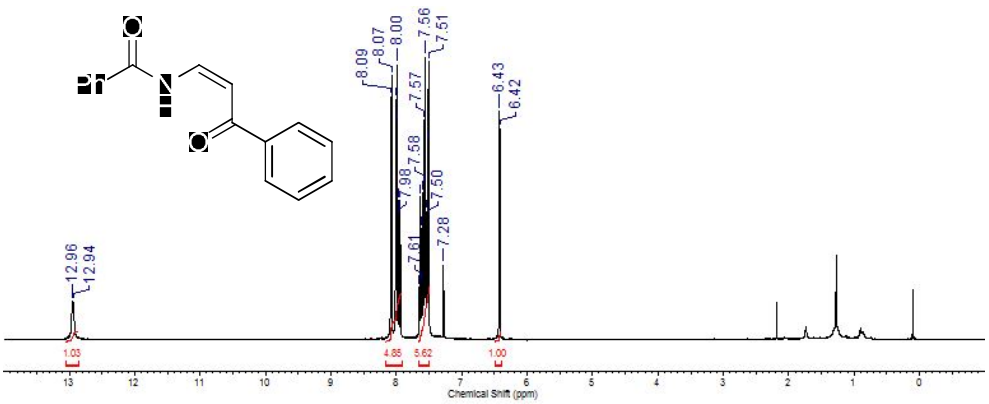


^{13}C NMR spectrum of **3ad** ($CDCl_3$)



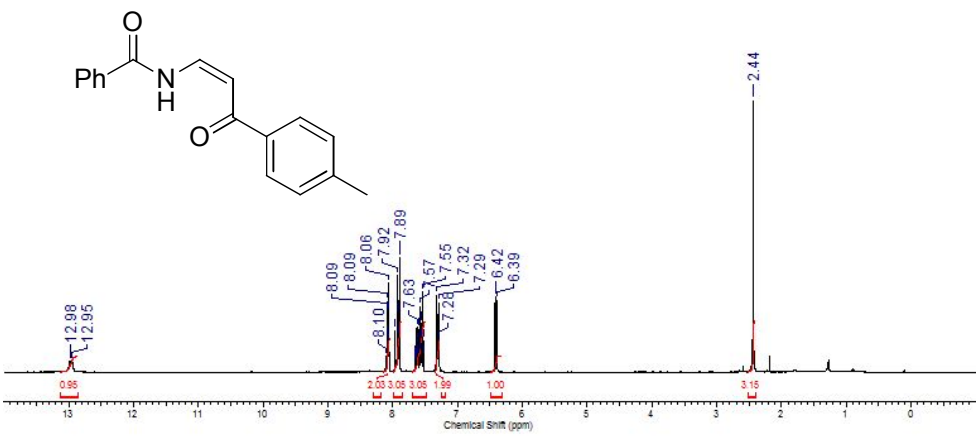
N-((*Z*)-3-oxo-3-phenylprop-1-enyl)benzamide (3ae)

^{1}H NMR spectrum of **3ae** ($CDCl_3$)

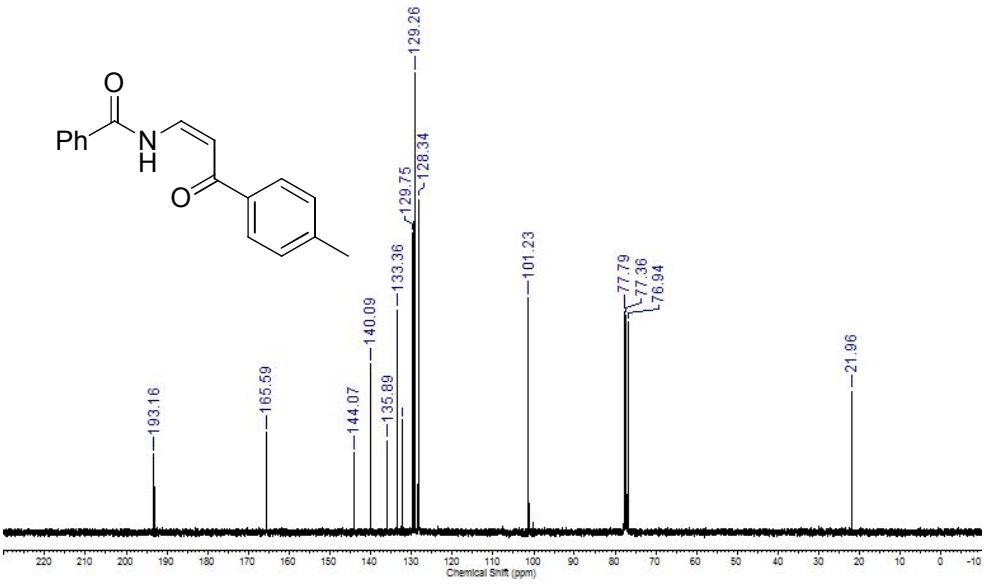


N-((*Z*)-3-oxo-3-(p-tolyl)prop-1-enyl)benzamide (3af)

^{1}H NMR spectrum of **3af** ($CDCl_3$)

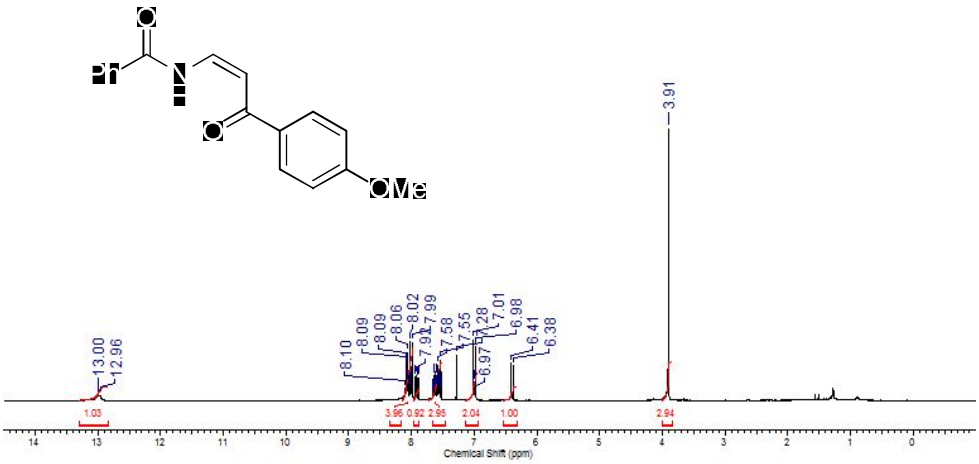


^{13}C NMR spectrum of **3af** ($CDCl_3$)



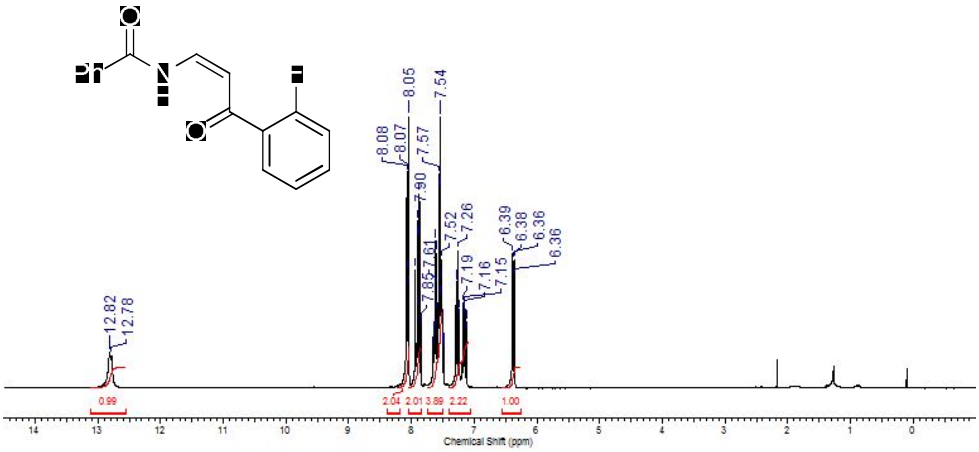
N-((*Z*)-3-(4-methoxyphenyl)-3-oxoprop-1-enyl)benzamide (3ag)

^{1}H NMR spectrum of **3ag** ($CDCl_3$)

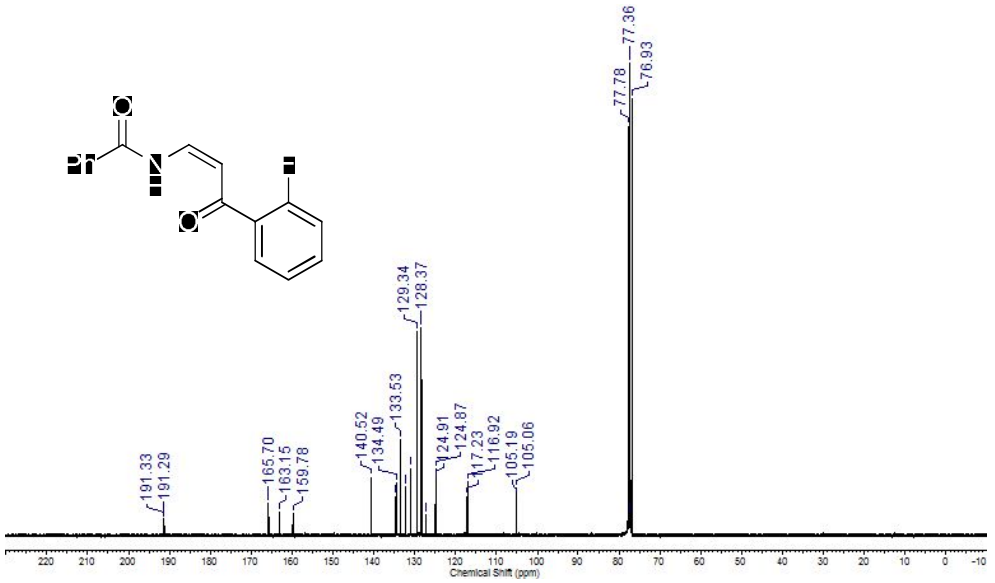


N-((*Z*)-3-(2-fluorophenyl)-3-oxoprop-1-enyl)benzamide (3ah)

^{1}H NMR spectrum of **3ah** ($CDCl_3$)

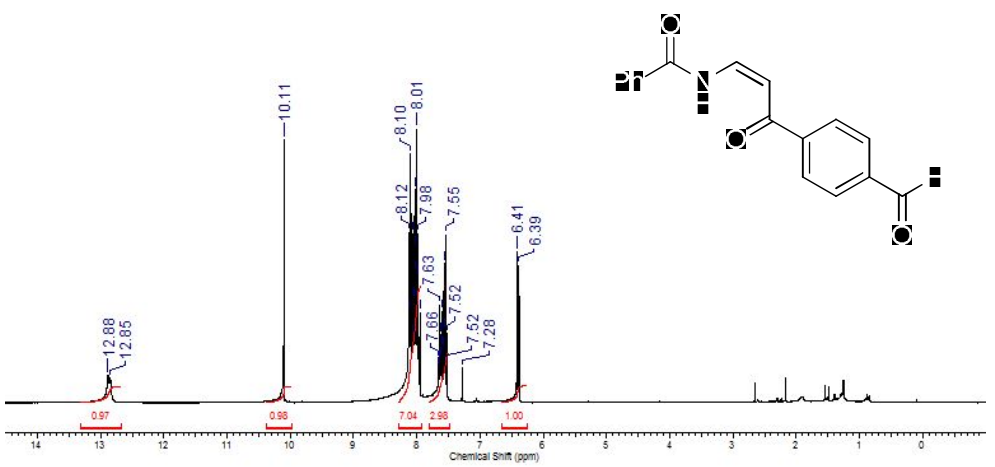


^{13}C NMR spectrum of **3ah** ($CDCl_3$)

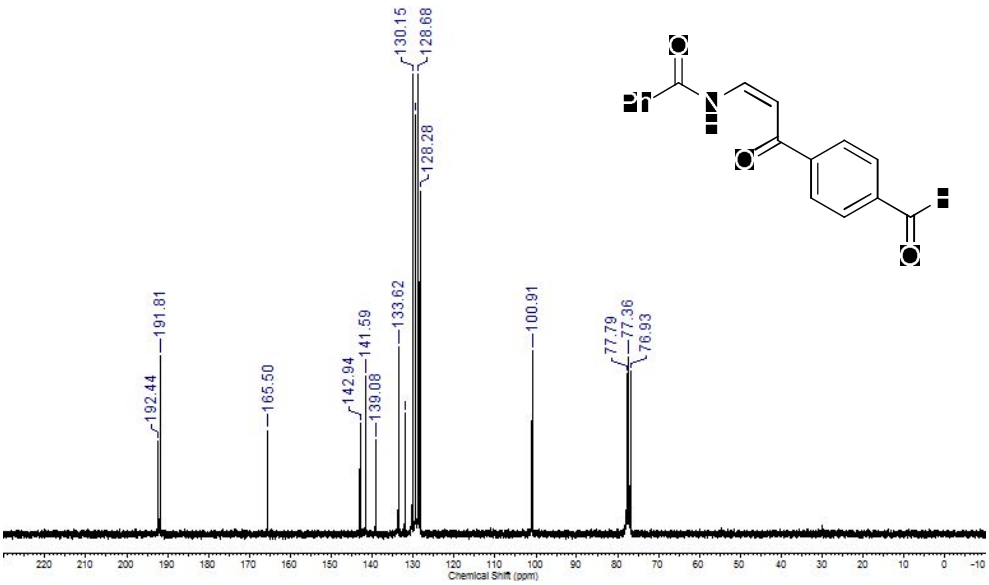


N-((*Z*)-3-(4-formylphenyl)-3-oxoprop-1-enyl)benzamide (3ai)

^{1}H NMR spectrum of **3ai** ($CDCl_3$)

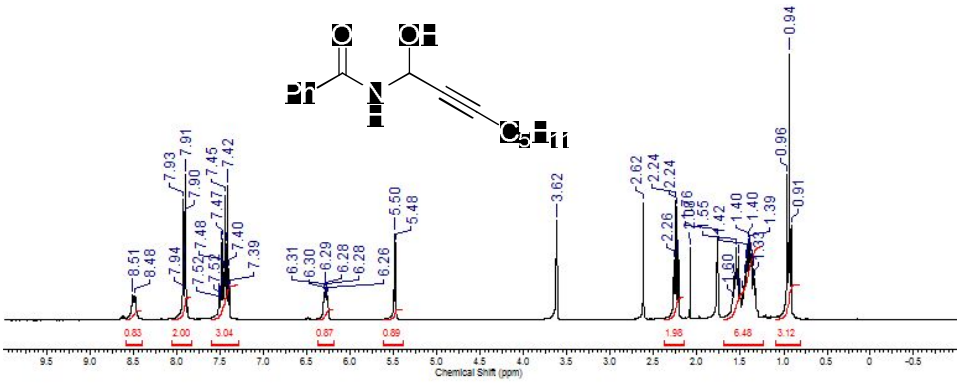


^{13}C NMR spectrum of **3ai** ($CDCl_3$)

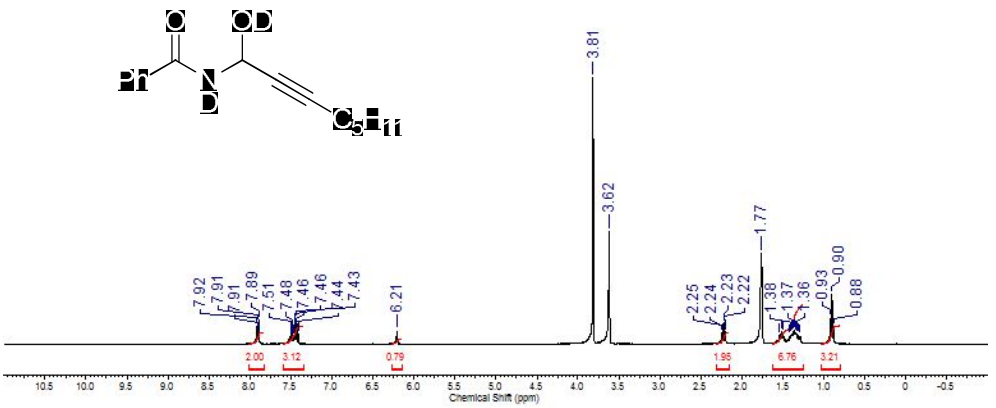


Hemiaminal 5, (*N*-(1-hydroxyoct-2-ynyl)benzamide)

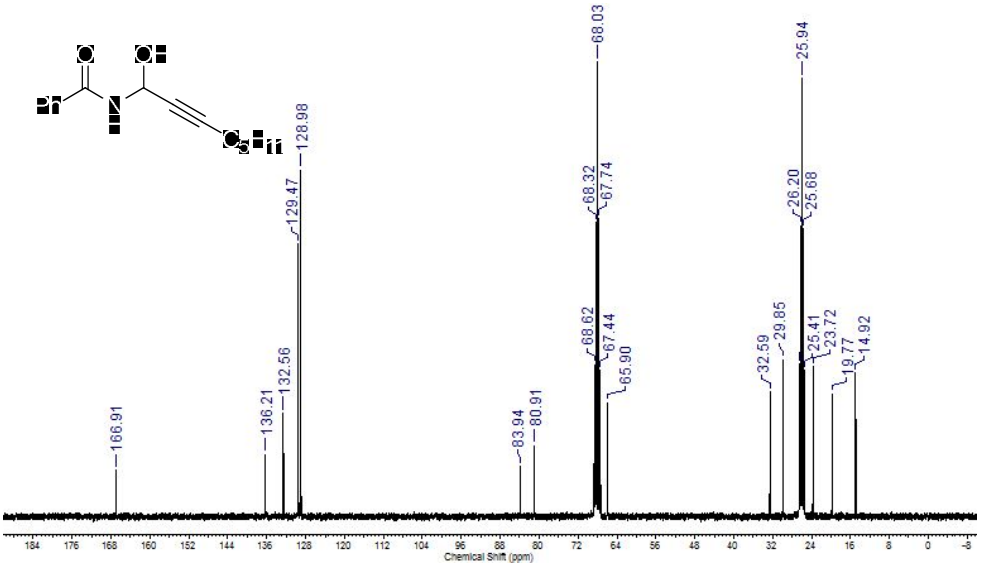
^{1}H NMR spectrum of **5** (THF-d_8)



^{1}H NMR spectrum of **5** (THF-d_8 + D_2O)



^{13}C NMR spectrum of **5** (THF-d_8)



요약

금 1가 촉매의 일련 작용으로 아마이드 첨가 반응, 마이어-슈스터 재배열 반응을 통해 엔아마이드를 일차 아마이드와 프로파질 알데하이드로부터 합성하는 새로운 전략을 개발하였다. 또한 엔아마이드의 스테레오화학은 반응 용매를 바꾸고 촉매 양의 산을 첨가할 때 간단하게 조절되었다. 새로이 개발된 전략은 β-치환된-α,β-불포화 카보닐 화합물을 보다 다양하게 합성할 수 있는 새로운 방법을 제시한다.

주요어 : 금 촉매 반응, 일련 작용, 엔아마이드, 스테레오화학

학 번 : 2014 - 20308